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Supporting Information

Azaphilic versus Carbophilic Coupling at C=N Bonds: Key Steps in Titanium-Assisted Multicomponent Reactions

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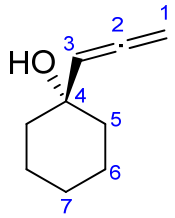
1. General Information

All manipulations, except those indicated, were carried out under exclusion of air and moisture using standard Schlenk and glove box techniques. As inert gas, Argon 5.0, purchased from Messer Group GmbH, was used after drying over Granusic© phosphorpentoxide granulate. Solvents were dried over activated alumina columns using a solvent purification system (M. Braun SPS 800) or according to standard literature methods[1] and stored in glass ampules under an argon atmosphere. Diethyl ether and *n*-pentane were distilled from sodium/potassium alloy, tetrahydrofuran, benzene and *n*-hexane from potassium, methanol from magnesium, dichloromethane, chloroform and triethylamine from calcium hydride and toluene from sodium. The same procedures were used to dry the deuterated solvents. NMR spectra were recorded on Bruker Avance (400 MHz, 600 MHz) instruments. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to residual proton solvent signals or carbon resonances.[2] H_3PO_4 (^{31}P) and CCl_3F (^{19}F) were used as external standards. The following abbreviations were used: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet), br (broad signal). High-resolution mass spectra were acquired on Bruker ApexQe hybrid 9.4 T FT-ICR (ESI) and JEOL JMS-700 magnetic sector (FAB, EI, LIFDI) spectrometers at the mass spectrometry facility of the Institute of Organic Chemistry, of the University of Heidelberg. Elemental analyses were carried out in the Microanalysis Laboratory of the Heidelberg Chemistry Department on a vario MICRO cube (Elementar*)*. IR spectra were acquired on a Varian 3100 FT IR spectrometer (Excalibur series) of a nujol mull of the compounds at room temperature using a KBr cell. HPLC analyses were conducted on a Agilent 1200 Series chromatograph using chiral Daicel columns (AD-H, OD-H or OJ-H). Notably, due to the multicomponent setup of the reactions, the highly reactive nature of the reactants and the variability of the concentrations of the Grignard solutions the yields were found to vary considerably in several cases. All other chemicals were obtained from commercial suppliers, dried under high vacuum or over molecular sieves and stored under an inert atmosphere.

2. Preparation of starting materials



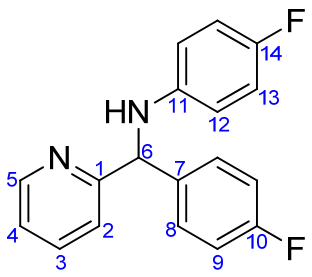
The cyclohexyl allenol was prepared following a standard literature method starting from 1-ethynyl-1-cyclohexanol, paraformaldehyde, dicyclohexylamine and anhydrous CuBr in dioxane.[3]

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 5.29 (t, *J*= 6.7 Hz, 1H, H-3), 4.87 (d, *J*= 6.7 Hz, 2H, H-1), 1.68-1.56 (m, 6H, H-5 + H-5‘ + H-6), 1.50-1.40 (m, 3H, H-6‘ + H-7), 1.39-1.30 (m, 1H, H-7‘);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 206.36 (s, C-2), 99.52 (s, C-3), 78.31 (s, C-1), 70.62 (s, C-4), 38.40 (s, C-5), 25.60 (s, C-7), 22.65 (s, C-6);

3. Preparation of *N*-aryl benzhydrylamines (Ar = Ar')

General procedure 1 (GP 1): To a solution of the indicated heteroaromatic nitrile (5.19 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the indicated Grignard reagent in THF (0.5-2 M, 3 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL) was added and the reaction mixture was placed in an oil bath and heated to 60 °C for 18 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ solution and filtered to remove insoluble metal salts. The residue was extracted with ethyl acetate and dichloromethane and the combined organic extracts were evaporated. Purification by column chromatography yielded the corresponding (2-pyridylmethyl)amines as oils or solids. Solid products can be obtained by crystallization from hot *n*-hexane:ethyl acetate mixtures at −30 °C.



5.19 mmol scale from 2-pyridinecarbonitrile, 4-fluorophenylmagnesium bromide (1 M in THF) and titanium(IV) isopropoxide (1.54 mL). **1a** was obtained as a yellow oil (63 %)

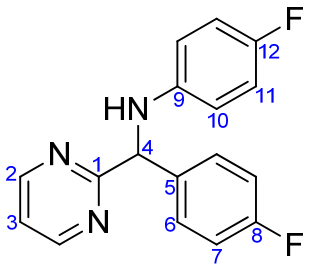
^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.61-8.58 (m, 1H, H-5), 7.70-7.66 (m, 1H, H-3), 7.45-7.41 (m, 2H, H-8), 7.35 (d, *J*= 7.9 Hz, 1H, H-2), 7.23-7.20 (m, 1H, H-4), 7.03-6.99 (m, 2H, H-9), 6.85-6.80 (m, 2H, H-13), 6.57-6.53 (m, 2H, H-12), 6.10-4.99 (bs, 1H, *N*H), 5.55 (s, 1H, H-6);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 296 K): δ [ppm] = 162.36 (d, *J*= 245.9 Hz, C-10), 160.42 (m, C-1), 156.12 (d, *J*= 235.6 Hz, C-14), 148.83 (m, C-5), 143.18 (d, *J*= 1.8 Hz, C-11), 137.91 (m, C-7), 137.69 (m, C-3), 129.10 (d, *J*= 8.2 Hz, C-8), 122.73 (s, C-4), 122.25 (s, C-2), 115.95 (d, *J*= 21.6 Hz, C-9), 115.75 (d, *J*= 22.4 Hz, C-13), 114.68 (d, *J*= 7.4 Hz, C-12), 62.91 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_6$, 376.27 MHz, 295 K): δ [ppm] = −114.57 (s, 1F, F-10), −127.49 (s, 1F, F-14);

Elemental analysis:	found:	C 72.71%,	H 4.90%,	N 9.44%,
calculated:	C 72.96%,	H 4.76%,	N 9.45%.	

MS (HR-ESI(+)):	m / z	297.1200	($[M+H]^+$)
calculated:	297.1203	($C_{18}H_{15}N_2F_2O$ ≙ $[M+H]^+$)	



2.67 mmol scale from 2-pyrimidinecarbonitrile in THF (8 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (0.79 mL). Purification by column chromatography (*n*-pentane:ethyl acetate = 20:1 to 3:1) (60 %) and recrystallization from hot *n*-hexane at −30 °C yielded colorless crystals of **1b**.

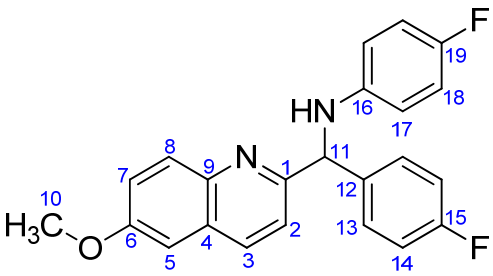
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.71 (d, *J*= 4.9 Hz, 2H, H-2), 7.58-7.50 (m, 2H, H-6), 7.17 (t, *J*= 4.9 Hz, 1H, H-3), 7.03-6.95 (m, 2H, H-7), 6.87-6.80 (m, 2H, H-11), 6.62-6.55 (m, 2H, H-10), 6.17-5.00 (bs, 1H, *N*H), 5.70 (s, 1H, H-4);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 299 K): δ [ppm] = 169.12 (m, C-1), 162.25 (d, *J*= 246.0 Hz, C-8), 157.29 (s, C-2), 155.86 (d, *J*= 235.4 Hz, C-12), 142.64 (d, *J*= 1.8 Hz, C-9), 136.67 (d, *J*= 3.1 Hz, C-5), 128.84 (d, *J*= 8.2 Hz, C-6), 119.51 (s, C-3), 115.70 (d, *J*= 8.9 Hz, C-7/11), 115.48 (d, *J*= 8.0 Hz, C-11/7), 114.42 (d, *J*= 7.5 Hz, C-10), 63.13 (s, C-4);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.23 MHz, 297 K): δ [ppm] = −114.84 (s, F-8), −127.72 (s, F-12);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 297 K): δ [ppm] = 285.4 (m, $N_{pyrimidine}$), 68.5 (m, N*H*);

MS (HR-ESI(+)):	m / z	298.1152	($[M+H]^+$)
	calculated:	298.1156	($C_{17}H_{14}N_3F_2$ ≙ $[M+H]^+$)



2.67 mmol scale from 6-methoxy-2-quinolinecarbonitrile in THF (24 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (0.79 mL). Purification by column chromatography (*n*-pentane:ethyl

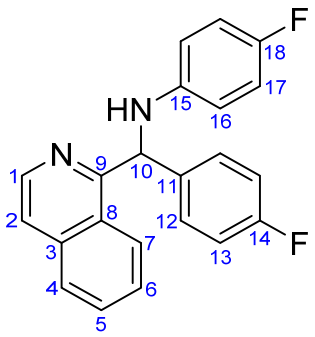
acetate = 50:1 to 10:1) (54 %). Crystallization from hot *n*-hexane at −30 °C yielded colorless crystals of **1c** suitable for X-ray diffraction analysis.

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.12-8.03 (m, 1H, H-8), 7.98 (d, *J*= 8.3 Hz, 1H, H-3), 7.53-7.46 (m, 2H, H-13), 7.42-7.38 (m, 1H, H-7), 7.32 (d, *J*= 7.9 Hz, H-2), 7.06-7.04 (m, 1H, H-5), 7.03-6.98 (m, 2H, H-14), 6.86-6.81 (m, 2H, H-18), 6.64-6.60 (m, 2H, H-17), 6.01 (bs, 1H, *N*H), 5.63 (s, 1H, H-11), 3.92 (s, 3H, H-10);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 162.33 (d, *J*= 246.1 Hz, C-15), 158.09 (s, C-6), 157.56 (s, C-1), 155.96 (d, *J*= 235.1 Hz, C-19), 143.35 (s, C_{Ar}), 143.07 (bs, C_{Ar}), 138.25 (bs, C_{Ar}), 136.19 (bs, C-3), 130.46 (bs, C-8), 129.25 (d, *J*= 8.1 Hz, C-13), 128.45 (s, C-4), 122.71 (bs, C-7), 120.26 (s, C-2), 115.93 (d, *J*= 21.5 Hz, C-14), 115.72 (d, *J*= 22.4 Hz, C-18), 114.57 (d, *J*= 7.4 Hz, C-17), 105.28 (s, C-5), 62.93 (s, C-11), 55.73 (s, C-10);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −114.75 (s, F-15), −127.98 (s, F-19);

MS (HR-ESI(+)): m / z 377.1463 ($[M+H]^+$)
calculated: 377.1465 ($C_{23}H_{19}N_2F_2O \triangleq [M+H]^+$)



3.00 mmol scale from 1-isoquinolinecarbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (888 µL). Purification by column chromatography (*n*-pentane:ethyl acetate = 30:1) (59 %) gave **1d** as a pale brown solid.

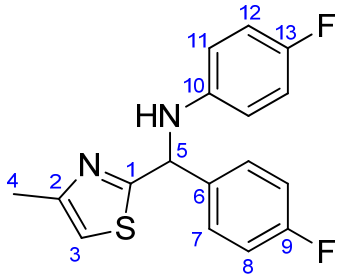
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.58 (d, *J*= 5.7 Hz, 1H, H-1), 8.37 (d, *J*= 8.1 Hz, 1H, H-4/7), 7.85-7.80 (m, 1H, H-4/7), 7.70-7.60 (m, 2H, H-5 + H-6), 7.62-7.53 (m, 3H, H-2 + H-12), 7.02-6.94 (m, 2H, H-13), 6.96-6.88 (m, 2H, H-17), 6.79-6.72 (m, 2H, H-16), 6.45 (s, 1H, H-10), 6.05 (bs, 1H, N*H*);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 297 K): δ [ppm] = 161.97 (d, *J*= 246.1 Hz, C-14), 159.11 (s, C-9), 155.89 (d, *J*= 235.2 Hz, C-18), 143.22 (d, *J*= 1.7 Hz, C-15), 141.31 (s, C-1), 137.52 (d, *J*= 3.1 Hz, C-11), 136.76 (s, C-3/8), 130.32 (s, C-5/6), 129.29 (d, *J*= 8.2 Hz, C-12), 127.82 (s, C-4/7), 127.78 (s, C-5/6), 125.67 (s, C-3/8), 124.23 (s, C-4/7), 120.76 (s, C-2), 115.71 (d, *J*= 22.3 Hz, C-13/17), 115.58 (d, *J*= 21.50 Hz, C-13/17), 114.64 (d, *J*= 7.4 Hz, C-16), 58.09 (s, C-10);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 296 K): δ [ppm] = −127.56 (s, F-18), −114.73 (s, F-14);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 296 K): δ [ppm] = 294.2 (m, $N_{isoquinoline}$), 74.3 (m, N*H*);

MS (HR-DART(+)): m / z 347.1351 ($[M+H]^+$)
calculated: 347.1360 ($C_{22}H_{17}N_2F_2$ ≙ $[M+H]^+$)



8.64 mmol scale from 4-methylthiazole-2-carbonitrile in THF (30 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (2.56 mL). Purification by column chromatography (*n*-pentane:ethyl acetate:triethylamine = 50:1:1) (60 %). Crystallization from hot *n*-hexane at −30 °C yielded colorless crystals of **1e** suitable for X-ray diffraction analysis.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 7.48-7.42 (m, 2H, H-7), 7.08-7.02 (m, 2H, H-8), 6.88-6.82 (m, 2H, H-12), 6.81-6.80 (m, 1H, H-3), 6.59-6.53 (m, 2H, H-11), 5.70-5.66 (m, H-5), 4.87-4.77 (m, 1H, *N*H), 2.44-2.43 (m, 3H, H-4);

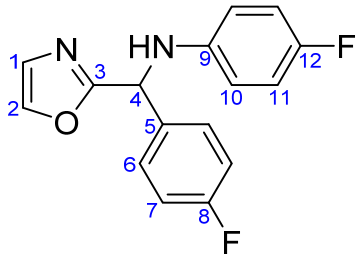
^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 172.76 (s, C-1), 162.58 (d, *J*= 247.2 Hz, C-9), 156.44 (d, *J*= 236.5 Hz, C-13), 153.15 (s, C-2), 142.92 (d, *J*= 2.0 Hz, C-10), 136.81 (d, *J*= 3.2 Hz, C-6), 129.08 (d, *J*= 8.3 Hz, C-7), 116.02 (d, *J*= 21.6 Hz, C-8), 115.70 (d, *J*= 22.4 Hz, C-12), 114.83 (d, *J*= 7.5 Hz, C-11), 114.16 (s, C-3), 61.05 (s, C-5), 17.20 (s, C-4);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −113.40 (s, F-9), −126.26 (s, F-13);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 296 K): δ [ppm] = 316.1 (m, $N_{Thiazole}$), 76.3 (m, N*H*);

Elemental analysis: found: C 64.80%, H 4.70%, N 8.93%,
calculated: C 64.54%, H 4.46%, N 8.85%.

MS (HR-ESI(+)): m / z 339.0742 ($[M+Na]^+$)
calculated: 339.0743 ($C_{17}H_{14}N_2F_2SNa$ ≙ $[M+Na]^+$)



2.66 mmol scale from 1,3-oxazole-2-carbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) isopropoxide (787 µL). Purification by column chromatography (*n*-pentane:ethyl acetate = 20:1) (55 %). **1f** was obtained as a yellow oil.

^{1}H-NMR (C_6D_6, 600.13 MHz, 295 K): δ [ppm] = 7.23-7.19 (m, 2H; H-6), 7.02-7.00 (m, 1H, H-1/2), 6.78-6.68 (m, 5H, H-1/2 + H-7 + H-11), 6.38-6.33 (m, 2H, H-10), 5.45 (d, *J*= 6.1 Hz, 1H, H-4), 5.19-5.15 (m, 1H, N-*H*);

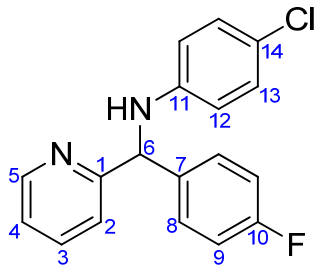
^{13}C{^{1}H}-NMR (C_6D_6, 100.55 MHz, 299 K): δ [ppm] = 163.89 (s, C-3), 162.84 (d, *J*= 246.2 Hz, C-8), 156.69 (d, *J*= 235.5 Hz, C-12), 143.07 (d, *J*= 1.8 Hz, C-9), 139.34 (s, C-1/2), 135.01 (d, *J*= 3.1 Hz, C-5), 129.24 (d, *J*= 8.2 Hz, C-6), 127.26 (s, C-1/2), 115.91 (d, *J*= 22.4 Hz, C-7/11), 115.89 (d, *J*= 21.6 Hz, C-7/11), 114.97 (d, *J*= 7.4 Hz, C-10), 56.52 (s, C-4);

^{19}F{^{1}H}-NMR (C_6D_6, 376.27 MHz, 298 K): δ [ppm] = −113.76 (m, 1F, F-8), −126.52 (m, 1H, F-12);

MS (HR-EI(+)): m / z 286.0914 ($[M]^+$)
calculated: 286.0918 ($C_{16}H_{12}N_2F_2O \triangleq [M]^+$)

4. Preparation of *N*-aryl benzhydrylamines (Ar ≠ Ar'))

General procedure 2 (GP 2): To a solution of the indicated *N*-heteroaromatic nitrile (5.19 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the indicated Grignard reagent in THF (0.5-2 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL) was added and the reaction mixture was stirred for 10 min. Then, the second Grignard reagent was added as a solution in THF (0.5-2 M, 2 eq) and the mixture was placed in an oil bath and heated to 60 °C for 18 h. The reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ solution and filtered to remove insoluble salts. The residue was extracted with ethyl acetate and dichloromethane and the combined organic extracts were evaporated. Purification by column chromatography on SiO_2, yielded the corresponding (2-pyridylmethyl)amines as oils or solids. Solid products can be obtained by crystallization from hot *n*-hexane:ethyl acetate mixtures at −30 °C.



2.67 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (10 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (790 µL, 1 eq) and 4-chlorophenylmagnesium bromide (1 M in Et_2O, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 50:1:1) (53 %). **2a** was obtained as a colorless solid.

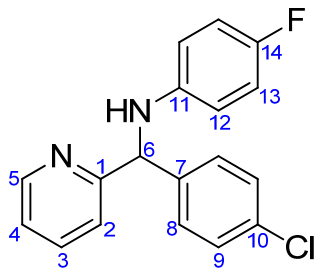
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.61-8.57 (m, 1H, H-5), 7.66-7.60 (m, 1H, H-3), 7.43-7.37 (m, 2H, H-8), 7.29 (d, *J*= 8.2 Hz, 1H, H-2), 7.21-7.16 (m, 1H, H-4), 7.08-7.04 (m, 2H, H-13), 7.03-6.98 (m, 2H, H-9), 6.56-6.51 (m, 2H, H-12), 5.64 (bs, 1H, *N*H), 5.51 (s, 1H, H-6);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 162.32 (d, *J*= 246.1 Hz, C-10), 160.14 (s, C-1), 149.34 (s, C-5), 145.43 (s, C-11), 137.99 (d, *J*= 3.2 Hz, C-7), 137.14 (s, C-3), 129.12 (s, C-13), 128.98 (d, *J*= 8.1 Hz, C-8), 122.62 (s, C-4), 122.34 (s, C-14), 122.08 (s, C-2), 115.95 (d, *J*= 21.6 Hz, C-9), 114.82 (s, C-12), 62.43 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −114.71 (s, F-10);

MS (HR-ESI(+)): m / z 313.0905 ($[M+H]^+$)

calculated: 313.0908 ($C_{18}H_{15}N_2FCl$ ≙ $[M+H]^+$)



5.34 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (20 mL), 4-chlorophenylmagnesium bromide (1 M in Et_2O, 1 eq), titanium(IV) isopropoxide (1.58 mL, 1 eq) and 4-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 30:1:1) (57 %). **2b** was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.59 (d, *J*= 4.7 Hz, 1H, H-5), 7.65-7.58 (m, 1H, H-3), 7.40 (d, *J*= 8.3 Hz, 2H, H-8), 7.32-7.27 (m, 3H, H-2 + H-9), 7.20-7.14 (m, 1H, H-4), 6.87-6.80 (m, 2H, H-13), 6.58-6.52 (m, 2H, H-12), 5.75-5.24 (bs, 1H, *N*H), 5.49 (s, 1H, H-6);

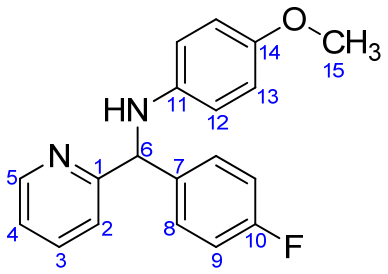
^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 160.07 (s, C-1), 155.96 (d, *J*= 235.1 Hz, C-14), 149.29 (s, C-5), 143.18 (d, *J*= 1.7 Hz, C-11), 140.99 (s, C-7), 137.06 (s, C-3), 133.38 (s, C-10), 129.10 (s, C-9), 128.73 (s, C-8), 122.57 (s, C-4), 122.03 (s, C-2), 115.67 (d, *J*= 22.3 Hz, C-13), 114.48 (d, *J*= 7.4 Hz, C-12), 62.99 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −127.60 (s),

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 302.7 (m, $N_{pyridine}$), 71.4 (m, N*H*);

MS (HR-ESI(+)): m / z 647.1547 ($[2M+Na]^+$)

calculated: 647.1557 ($C_{36}H_{28}N_4F_2Cl_2Na$ ≙ $[2M+Na]^+$)



10.4 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (30 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (3.07 mL, 1 eq) and 4-methoxyphenylmagnesium bromide (0.5 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 100:1 to 9:1) (49 %). **2c** was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 8.62-8.58 (m, 1H, H-5), 7.64-7.57 (m, 1H, H-3), 7.48-7.41 (m, 2H, H-H-8), 7.36-7.32 (m, 1H, H-2), 7.18-7.13 (m, 1H, H-4), 7.05-6.98 (m, 2H, H-9), 6.78-6.73 (m, 2H, H-13), 6.4-6.59 (m, 2H, H-12), 5.54 (d, *J*= 4.3 Hz, 1H, H-6), 5.22 (d, *J*= 4.3 Hz, 1H, *N*H), 3.71 (s, 3H, H-15);

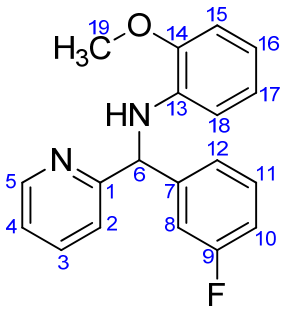
^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 162.09 (d, *J*= 245.9 Hz, C-10), 160.92 (s, C-1), 152.19 (s, C-11/14), 149.25 (s, C-5), 141.15 (s, C-14/11), 138.49 (d, *J*= 3.1 Hz, C-7), 136.89 (s, C-3), 129.01 (d, *J*= 8.1 Hz, C-8), 122.30 (s, C-4), 121.85 (s, C-2), 115.64 (d, *J*= 21.5 Hz, C-9), 114.90 (s, C-12/13), 114.79 (s, C-13/12), 63.37 (s, C-6), 55.66 (s, C-15);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −114.95 (s, F-10);

^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 304.0 (m, $N_{pyridine}$), 70.2 (m, N*H*);

Elemental analysis:	found:	C 73.99%,	H 5.86%,	N 9.00%,
	calculated:	C 74.01%,	H 5.56%,	N 9.08%.

MS (HR-ESI(+)):	m / z	309.1399	($[M+H]^+$)
	calculated:	309.1403	($C_{19}H_{18}N_2FO$ ≙ $[M+H]^+$)



5.2 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (20 mL), 3-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and 2-methoxyphenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 100:1:1) (52 %). **2d** was obtained as a pale yellow oil.

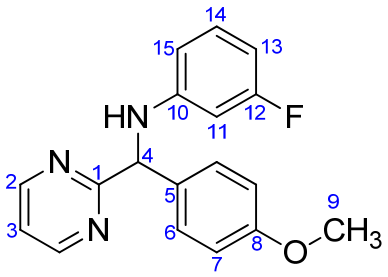
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.63 (d, *J*= 4.7 Hz, 1H, H-5), 7.66-7.60 (m, 1H, H-3), 7.39 (d, *J*= 7.8 Hz, 1H, H-2), 7.32-7.27 (m, 2H, H-11 + H-12), 7.23-7.15 (m, 2H, H-4 + H-8), 6.98-6.91 (m, 1H, H-10), 6.82 (d, *J*= 7.8 Hz, 1H, H-15), 6.79-6.73 (m, 1H, H-17), 6.72 6.66 (m, 1H, H-16), 6.44 (d, *J*= 7.7 Hz, 1H, H-18), 5.84 (d, *J*= 4.7 Hz, 1H, *N*H), 5.61 (d, *J*= 4.7 Hz, 1H, H-6), 3.91 (s, 3H, H-19);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 299 K): δ [ppm] = 163.25 (d, *J*= 246.2 Hz, C-9), 160.71 (s, C-1), 149.55 (s, C-5), 147.20 (s, C-14), 145.36 (d, *J*= 6.6 Hz, C-7), 137.01 (s, C-3), 136.77 (s, C-13), 130.35 (d, *J*= 8.2 Hz, C-11), 123.13 (d, *J*= 2.8 Hz, C-12), 122.46 (s, C-4), 121.80 (s, C-2), 121.13 (s, C-17), 117.10 (s, C-16), 114.52 (d, *J*= 21.3 Hz, C-10), 114.33 (d, *J*= 22.0 Hz, C-8), 111.13 (s, C-18), 109.50 (s, C-15), 63.04 (d, *J*= 1.6 Hz, C-6), 55.54 (s, C-19);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 298 K): δ [ppm] = −112.35 (s, F-9);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 297 K): δ [ppm] = 304.7 (m, $N_{pyridine}$), 63.9 (m, N*H*);

MS (HR-ESI(+)):	m / z	309.1399	($[M+H]^+$)
	calculated:	309.1403	($C_{19}H_{18}N_2FO$ ≙ $[M+H]^+$)



5.2 mmol scale according to **GP 2**, from 2-pyrimidinecarbonitrile in THF (15 mL), 4-methoxyphenylmagnesium bromide (0.5 M in THF, 1 eq), titanium(IV) isopropoxide (1.65 mL, 1 eq) and 3-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 90:10:1) (56 %). **2e** was obtained as a pale yellow/brown oil.

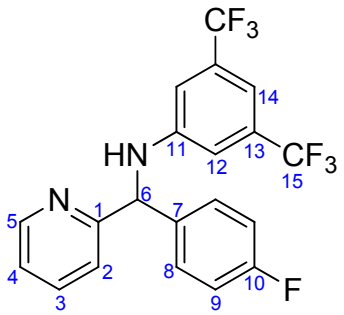
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.71 (d, *J*= 4.8 Hz, 2H, H-2), 7.48 (d, *J*= 8.5 Hz, 2H, H-6), 7.15 (t, *J*= 4.8 Hz, 1H, H-3), 7.08-7.01 (m, 1H, H-14), 6.85 (d, *J*= 8.5 Hz, 2H, H-7), 6.48-6.43 (m, 1H, H-15), 6.38-6.31 (m, 2H, H-11 + H-13), 5.70 (s, 1H, H-4), 3.75 (s, 3H, H-9);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 169.38 (s, C-1), 164.07 (d, *J*= 242.2 Hz, C-12), 159.25 (s, C-8), 157.43 (s, C-2), 148.40 (d, *J*= 10.9 Hz, C-10), 132.81 (s, C-5), 130.30 (d, *J*= 10.2 Hz, C-14), 128.43 (s, C-6), 119.55 (s, C-3), 114.28 (s, C-7), 109.55 (d, *J*= 2.1 Hz, C-15), 103.95 (d, *J*= 21.6 Hz, C-11/13), 100.44 (d, *J*= 25.4 Hz, C-13/11), 62.68 (s, C-4), 55.32 (s, C-9);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −112.91 (s);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 285.4.0 (m, $N_{pyrimidine}$), 73.7 (m, N*H*);

MS (HR-ESI):	m / z	641.2440	($[2M+Na]^+$)
	calculated:	641.2453	($C_{36}H_{32}N_6F_2O_2Na$ ≙ $[2M+Na]^+$)



3.1 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (15 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (0.92 mL, 1 eq) and 3,5-bis(trifluoromethyl)phenylmagnesium bromide (0.5 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 50:1:1) (28 %). **2f** was obtained as a pale yellow oil. Pale yellow bushy crystals are obtained upon cooling a hot saturated solution of the compound in *n*-hexane to −30 °C.

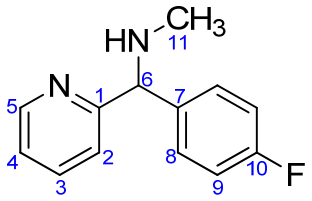
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.61 (d, *J*= 4.8 Hz, 1H, H-5), 7.69-7.63 (m, 1H, H-3), 7.47-7.41 (m, 2H, H-8), 7.27-7.20 (m, 2H, H-2 + H-4), 7.12 (s, 1H, H-14), 7.07-7.01 (m, 2H, H-9), 6.99 (s, 2H, H-12), 6.56 (bs, 1H, *N*H), 5.57 (s, 1H, H-6);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 162.49 (d, *J*= 246.6 Hz, C-10), 158.75 (s, C-1), 149.08 (s, C-5), 147.38 (s, C-11), 137.29 (s, C-3), 137.13 (d, *J*= 3.2 Hz, C-7), 132.36 (q, *J*= 32.8 Hz, C-13), 128.90 (d, *J*= 8.2 Hz, C-8), 123.62 (q, *J*= 272.7 Hz, C-15), 122.88 (s, C-2/4), 122.33 (s, C-4/2), 116.21 (d, *J*= 21.7 Hz, C-9), 112.86 (m, C-12), 110.45 (m, C-14), 61.41 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −63.23 (s, 6F, F-15), −114.02 (s, 1F, F-10);

^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 300.3 (m, $N_{pyridine}$), 78.3 (m, N*H*);

Elemental analysis:	found:	C 58.20%,	H 3.44%,	N 6.50%,
	calculated:	C 57.98%,	H 3.16%,	N 6.76%.
MS (HR-ESI(+)):	m / z	415.1040	($[M+H]^+$)	
	calculated:	415.1045	($C_{20}H_{14}N_2F_7$ ≙ $[M+H]^+$)	



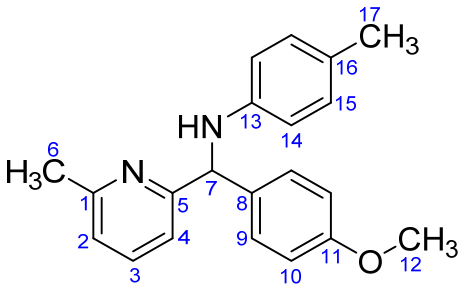
5.2 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (20 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and methylmagnesium chloride (22 wt% in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 6:1) (28 %). **2g** was obtained as a yellow/orange oil.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.56 (d, *J*= 4.7 Hz, 1H, H-5), 7.63-7.57 (m, 1H, H-3), 7.42-7.36 (m, 2H, H-8), 7.26 (d, *J*= 7.8 Hz, 1H, H-2), 7.15-7.11 (m, 1H, H-4), 7.03-6.96 (m, 2H, H-9), 4.78 (s, 1H, H-6), 2.40 (s, 3H, H-11);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 162.28 (s, C-1), 162.19 (d, *J*= 245.4 Hz, C-10), 149.40 (s, C-5), 138.29 (d, *J*= 3.2 Hz, C-7), 136.78 (s, C-3), 129.36 (d, *J*= 8.0 Hz, C-8), 122.23 (s, C-4), 121.89 (s, C-2), 115.48 (d, *J*= 21.3 Hz, C-9), 69.75 (s, C-6), 34.91 (s, C-11);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −115.50 (s);

MS (HR-ESI(+)):	m / z	217.1136	($[M+H]^+$)
	calculated:	217.1141	($C_{13}H_{14}N_2F$ ≙ $[M+H]^+$)



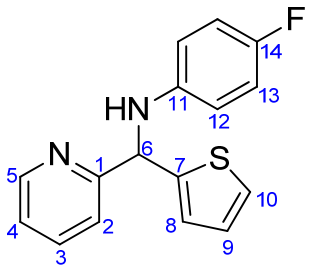
2 mmol scale according to **GP 2**, from 6-methylpyridine-2-carbonitrile in THF, 4-methoxyphenylmagnesium bromide (0.5 M in THF, 1 eq), titanium(IV) isopropoxide (0.6 mL, 1 eq) and *para*-tolylmagnesium chloride (2M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 30:1) (56 %). **2h** was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 7.55-7.51 (m, 1H, H-3), 7.48-7.45 (m, 2H, H-9), 7.23 (d, *J*= 7.8 Hz, 1H, H-4), 7.06-7.02 (m, 3H, H-2 + H-15), 6.95-6.92 (m, 2H, H-10), 6.69-6.65 (m, 2H, H-14), 5.60 (s, 1H, H-7), 5.46 (bs, 1H, N*H*), 3.80 (s, 3H, H-12), 2.66 (s, 3H, H-6), 2.31 (s, 3H, H-17);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 160.57 (s, C-5), 158.77 (s, C-11), 157.74 (s, C-1), 144.90 (s, C-16), 136.93 (s, C-3), 134.92 (s, C-8), 129.54 (s, C-15), 128.54 (s, C-9), 126.27 (s, C-13), 121.57 (s, C-2), 118.66 (s, C-4), 114.02 (s, C-10), 113.72 (s, C-14), 62.73 (s, C-7), 55.08 (s, C-12), 24.47 (s, C-6), 20.38 (s, C-17);

^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 303.5 (m, $N_{pyridine}$), 73.9 (m, *N*H);

MS (HR-DART(+)):	m / z	319.1802	($[M+H]^+$)
	calculated:	319.1810	($C_{21}H_{23}N_2O$ ≙ $[M+H]^+$)



10.4 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (30 mL), 2-thienylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (3.07 mL, 1 eq) and 4-fluorophenylmagnesium bromide (1 M in THF, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 30:1:1 to 9:1:1) (50 %). **2i** was obtained as a yellow/brown oil that crystallizes upon standing as an ocre solid. Crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in *n*-hexane at −30 °C.

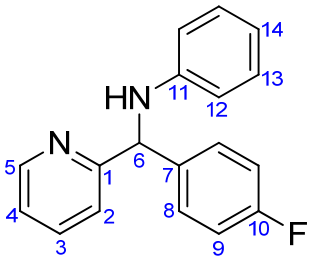
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.61 (d, *J*= 4.7 Hz, 1H, H-5), 7.66-7.7.60 (m, 1H, H-3), 7.40 (d, *J*= 7.9 Hz, 1H, H-2), 7.22-7.15 (m, 2H, H-4 + H-8/10), 7.06-7.03 (m, 1H, H-10/8), 6.97-6.93 (m, 1H, H-9), 6.90-6.82 (m, 2H, H-13), 6.68-6.61 (m, 2H, H-12), 5.82 (d, *J*= 5.1 Hz, 1H, H-6), 5.48 (d, *J*= 5.1 Hz, 1H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 160.07 (s, C-1), 156.09 (d, *J*= 235.7 Hz, C-14), 149.16 (s, C-5), 146.90 (s, C-7), 143.13 (d, *J*= 1.9 Hz, C-11), 137.05 (s, C-3), 126.87 (s, C-9), 125.24 (s, C-8/10), 125.09 (s, C-10/8), 122.63 (s, C-4), 121.71 (s, C-2), 115.59 (d, *J*= 22.3 Hz, C-13), 114.80 (d, *J*= 7.4 Hz, C-12), 59.61 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −127.07 (s);

Elemental analysis:	found:	C 67.85%,	H 4.47%,	N 9.98%,
	calculated:	C 67.58%,	H 4.61%,	N 9.85%.

MS (HR-ESI(+)):	m / z	591.1461	($[2M+Na]^+$)
	calculated:	591.1465	($C_{32}H_{26}N_4F_2S_2Na$ ≙ $[2M+Na]^+$).



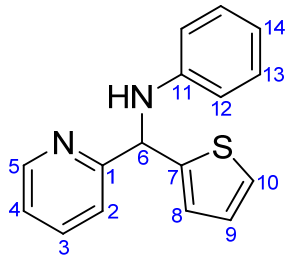
5.2 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (20 mL), 4-fluorophenylmagnesium bromide (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and phenyllithium (1.8 M in Bu_2O, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 50:1:1) (63 %). **2j** was obtained as a colorless oil .

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.64-8.61 (m, 1H, H-5), 7.66-7.61 (m, 1H, H-3), 7.49-7.44 (m, 2H, H-8), 7.36 (d, *J*= 7.9 Hz, 1H, H-2), 7.20-7.15 (m, 3H, H-4 + H-13), 7.06-7.01 (m, 2H, H-9), 6.76-6.71 (m, 1H, H-14), 6.69-6.65 (m, 2H, H-12), 5.61 (s, 1H, H-6), 5.55 (bs, 1H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 162.15 (d, *J*= 245.9 Hz, C-10), 160.59 (s, C-1), 149.30 (s, C-5), 146.88 (s, C-11), 138.36 (d, *J*= 3.1 Hz, C-7), 136.99 (s, C-3), 129.22 (s, C-13), 128.99 (d, *J*= 8.1 Hz, C-8), 122.41 (s, C-4), 121.93 (s, C-2), 117.68 (s, C-14), 115.75 (d, *J*= 21.5 Hz, C-9), 113.67 (s, C-12), 62.49 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −114.91 (s, F-10);

MS (HR-ESI(+)):	m / z	279.1294	($[M+H]^+$)
	calculated:	279.1298	($C_{18}H_{16}N_2F$ ≙ $[M+H]^+$)



5.2 mmol scale according to **GP 2**, from 2-pyridinecarbonitrile in THF (20 mL), 2-thienyllithium (1 M in THF, 1 eq), titanium(IV) isopropoxide (1.54 mL, 1 eq) and phenyllithium (1.8 M in Bu_2O, 2 eq). Purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 50:1:1) (43 %). **2k** was obtained as a yellow oil .

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.65-8.63 (m, 1H, H-5), 7.68-7.64 (m, 1H, H-3), 7.46 (d, *J*= 7.9 Hz, 1H, H-2), 7.24-7.22 (m, 1H, H-10), 7.22-7.16 (m, 3H, H-4 + H-13), 7.08-7.05 (m, 1H, H-8), 6.99-6.96 (m, 1H, H-9), 6.78-6.72 (m, 3H, H-12 + H-4), 5.93-5.90 (m, 1H, H-6), 5.54-5.49 (m, 1H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 160.34 (s, C-1), 149.24 (s, C-5), 146.99 (s, C-7), 146.74 (s, C-11), 137.07 (s, C-3), 129.20 (s, C-13), 126.87 (s, C-9), 125.21 (s, C-8/10), 125.07 (s, C-10/8), 122.60 (s, C-4), 121.65 (s, C-2), 118.05 (s, C-14), 113.86 (s, C-12), 59.11 (s, C-6);

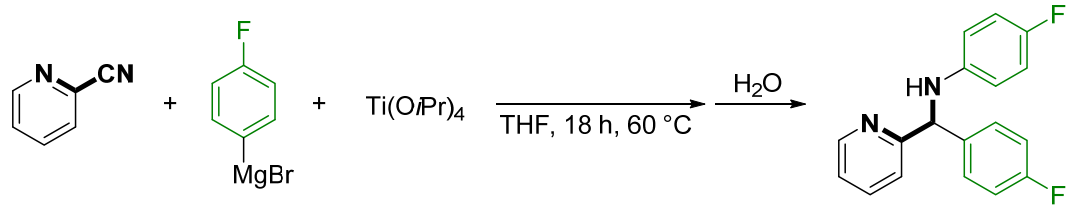
^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 304.0 (m, $N_{pyridine}$), 78.1 (m, N*H*);

MS (HR-EI(+)):	m / z	266.0895	($[M]^+$)
	calculated:	266.0878	($C_{16}H_{14}N_2S \mathrel{\widehat{=}} [M]^+$)

5. Alternative procedure

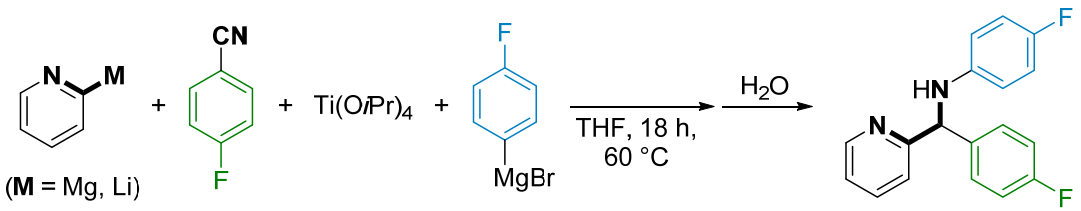
For several *N*-heterocyclic aromatics the desired nitrile compounds are conveniently accessible by a wide range of methods. Nevertheless, a complementary route is outlined below, relying on simple aromatic nitriles and metallated (Mg, Li) heterocycles. The latter may be prepared *in situ*, e.g. by direct or directed metalation or halogen-metal exchange, thus extending the scope of this procedure considerably. However, since this route requires a correct stoichiometry for four components, yields may decrease on smaller reaction scales.

Method A:



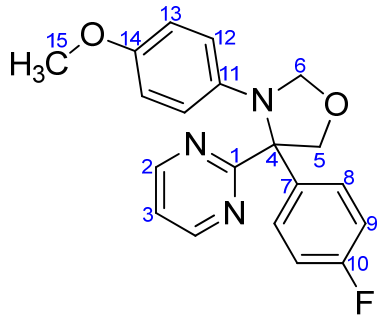
(1 eq.) (3 eq.) (1 eq.)

Method B:



(1 eq.) (1 eq.) (1 eq.) (2 eq.)

6. Characterization of the multi-component reaction products



To a solution of 2-pyrimidinecarbonitrile (5.6 mmol, 1 eq) in dry Et_2O (24 mL) at 0 °C was added a solution of the 4-fluorophenylmagnesium bromide in THF (1 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.65 mL, 1 eq) was added and the reaction mixture was stirred for 10 min. Then, 4-methoxyphenylmagnesium bromide was added as a solution in THF (0.5 M in THF, 2 eq) and the mixture was placed in an oil bath and heated to 40 °C for 18 h. To the reaction mixture dry paraformaldehyde (5 eq) was added in one portion and heating at 40 °C was continued overnight. The reaction was quenched by the addition of dest. water and filtered to remove insoluble metal salts. The byproduct 4-methoxybenzyl alcohol was removed from the reaction mixture by distillation *in vacuo*. The residue was purified by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 9:1:1) and **5a** was obtained as a yellow oil (33 %). Single crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in *n*-hexane at −30 °C.

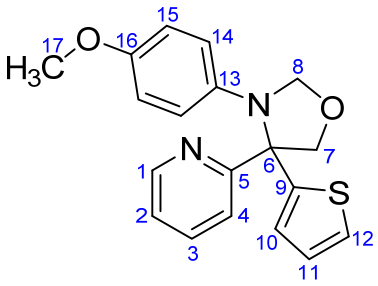
^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.69 (d, *J*=4.7 Hz, 2H, H-2), 7.45-7.41 (m, 2H, H-8), 7.10 (t, *J*= 4.7 Hz, 1H, H-3), 7.06-7.01 (m, 2H, H-9), 6.60 (d, *J*= 8.6 Hz, 2H, H-13), 6.38 (d, *J*= 8.6 Hz, 2H, H-12), 5.40 (s, 1H, H-6), 5.35 (s, 1H, H-6‘), 5.11 (d, *J*= 8.0 Hz, 1H, H-5), 4.40 (d, *J*= 8.0 Hz, 1H, H-5’), 3.66 (s, 3H, H-15);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 169.89 (s, C-1), 161.89 (d, *J*= 246.3 Hz, C-10), 156.69 (s, C-2), 151.90 (s, C-14), 137.49 (s, C-11), 136.22 (d, *J*= 3.1 Hz, C-7), 130.23 (d, *J*= 8.0 Hz, C-8), 119.25 (s, C-3), 115.42 (s, C-12), 114.67 (d, *J*= 21.3 Hz, C-9), 114.09 (s, C-13), 84.72 (s, C-5), 84.04 (s, C-6), 73.84 (s, C-4), 55.44 (s, C-15);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 298 K): δ [ppm] = −115.71 (s);

^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 295.75 (m, $N_{pyrimidine}$), 85.68 (m, $N_{oxazolidine}$);

MS (HR-ESI(+)):	m / z	352.1480	($[M+H]^+$)
	calculated:	352.1461	($C_{20}H_{20}N_3FO_2$ ≙ $[M+H]^+$)



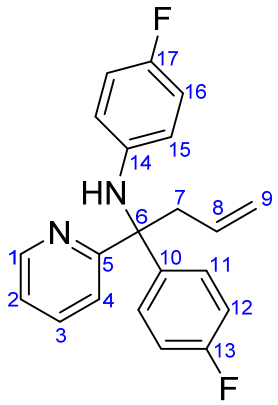
To a solution of 2-pyridinecarbonitrile (5.2 mmol, 1 eq) in dry THF (24 mL) at 0 °C was added a solution of the 2-thienylmagnesium bromide in THF (1 M, 1 eq) and the mixture was stirred 1 h at room temperature. Next, titanium(IV) isopropoxide (1.54 mL, 1 eq) was added and the reaction mixture was stirred for 10 min. Then, 4-methoxyphenylmagnesium bromide was added as a solution in THF (0.5 M in THF, 2 eq) and the mixture was placed in an oil bath and heated to 60 °C for 18 h. To the reaction mixture dry paraformaldehyde (5 eq) was added in one portion and stirring at room temperature was continued overnight. The reaction was quenched by the addition of dest. water and filtered to remove insoluble metal salts. The byproduct 4-methoxybenzyl alcohol was removed from the reaction mixture by distillation *in vacuo*. The residue was purified by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 50:1 to 9:1) and **5b** was obtained as a yellow oil (35 %).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.73-8.70 (m, 1H, H-1), 7.65-7.59 (m, 1H, H-3), 7.42-7.38 (m, 1H, H-4), 7.25-7.19 (m, 2H, H-2 + H-10/12), 6.99-6.96 (m, 1H, H-10/12), 6.90-6.87 (m, 1H, H-11), 6.70-6.64 (m, 2H, H-15), 6.35-6.30 (m, 2H, H-14), 5.40 (d, *J*= 2.1 Hz, 1H, H-8), 5.34 (d, *J*= 2.1 Hz, 1H, H-8'), 4.69 (d, *J*= 8.3 Hz, 1H, H-7), 4.44 (d, *J*= 8.3 Hz, 1H, H-7'), 3.69 (s, 3H, H-17).

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 160.69 (s, C-5), 152.02 (s, C-16), 148.92 (s, C-1), 144.27 (s, C-9), 136.91 (s, C-13), 136.70 (s, C-3), 127.42 (s, C-10/12), 126.26 (s, C-11), 126.01 (s, C-10/12), 122.53 (s, C-2), 122.29 (s, C-4), 115.57 (s, C-14), 114.37 (s, C-15), 84.82 (s, C-7), 83.64 (s, C-8), 70.94 (s, C-6), 55.58 (s, C-17).

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 310.2 (m, $N_{pyridine}$), 83.2 (m, N*H*);

MS (HR-DART(+)):	m / z	339.1164	($[M+H]^+$)
	calculated:	339.1167	($C_{19}H_{19}N_2O_2S$ ≙ $[M+H]^+$)



To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M in THF, 5.2 mL, 1 eq) in THF and the resulting mixture was stirred 1 h at room temperature. To the resulting suspension was added [Ti(O*i*Pr)$_4$] (1.54 mL, 1 eq) and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 10.4 mL, 2 eq) in THF and subsequently allyl bromide (0.9 mL 2 eq). The reaction mixture was heated to 60 °C overnight (*ca.* 18 h) and then quenched by the addition of an aqueous saturated NH_4Cl solution. Filtration, evaporation of the solvent and purification by column chromatography (SiO_2, petrol ether:ethyl acetate:triethylamine = 100:1:1) gave **6a** (1.01 g, 58 %) as a pale yellow oil.

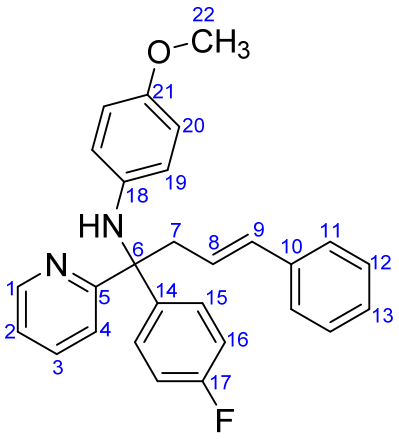
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.59-8.56 (m, 1H, H-1), 7.60-7.53 (m, 3H, H-3 + H-11), 7.16-7.12 (m, 1H, H-2), 7.09-7.00 (m, 3H, H-4 + H-12), 6.77-6.70 (m, 2H, H-16), 6.58 (bs, 1H, N*H*), 6.41-6.35 (m, 2H, H-15), 5.45-5.33 (m, 1H, H-8), 4.87-4.82 (m, 1H, H-9), 4.74-4.67 (m, 1H, H-9), 3.56-3.48 (m, 1H, H-7), 3.18-3.11 (m, 1H, H-7');

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 162.70 (s, C-5), 161.95 (d, *J*= 246.3 Hz, C-13), 155.73 (d, *J*= 234.9 Hz, C-17), 147.22 (s, C-1), 141.61 (d, *J*= 1.9 Hz, C-10/14), 141.50 (d, *J*= 3.2 Hz, C-14/10), 136.85 (s, C-3), 132.63 (s, C-8), 128.99 (d, *J*= 7.9 Hz, C-11), 122.24 (s, C-4), 121.84 (s, C-2), 118.77 (s, C-9), 116.21 (d, *J*= 7.2 Hz, C-15), 115.74 (d, *J*= 21.2 Hz, C-12), 115.34 (d, *J*= 22.1 Hz, C-16), 64.00 (s, C-6), 40.74 (s, C-7);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −115.62 (s, F-13), −128.47 (s, F-17);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 300.6 (m, $N_{pyridine}$), 72.5 (m, N*H*);

MS (HR-DART(+)):	m / z	337.1508	($[M+H]^+$)
	calculated:	337.1516	($C_{21}H_{19}N_2F_2$ ≙ $[M+H]^+$)



To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M in THF, 5.2 mL, 1 eq) in THF and the resulting mixture was stirred 1 h at room temperature. To the resulting suspension was added [Ti(O*i*Pr)$_4$] (1.54 mL, 1 eq) and, after 10 min, a solution of 4-methoxyphenylmagnesium bromide (0.5 M, 20.8 mL, 2 eq) in THF and subsequently cinnamyl bromide (1.54 mL 2 eq). The reaction mixture was heated to 60 °C overnight (*ca.* 18 h) and then quenched by the addition of an aqueous saturated NH_4Cl solution. Filtration, evaporation of the solvent and purification by column chromatography (SiO_2, petrol ether:ethyl acetate:triethylamine = 100:1:1) gave **6b** (34 %) as a yellow foam.

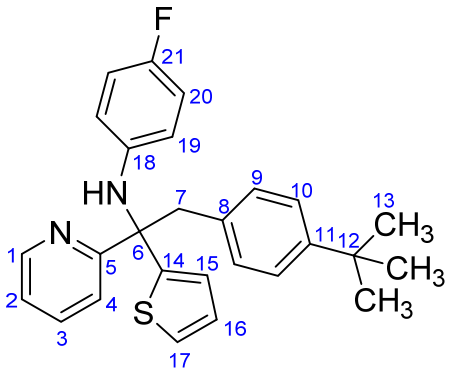
^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.72-8.70 (m, 1H, H-1), 7.80-7.76 (m, 2H, H-15), 7.73-7.69 (m, 1H, H-3), 7.39-7.35 (m, 2H, H-12), 7.34-7.23 (m, 5H, H-2 + H-4 + H-11 + H-13), 7.23-7.18 (m, 2H, H-16), 6.83-6.80 (m, 2H, H-20), 6.60-6.57 (m, 2H, H-19), 6.42 (bs, 1H, N*H*), 6.15 (d, *J*= 15.9 Hz, 1H, H-9), 5.96-5.89 (m, 1H, H-8), 3.86 (s, 3H, H-22), 3.82-3.77 (m, 1H, H-7), 3.48-3.43 (m, 1H, H-7');

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 163.11 (s, C-5), 161.85 (d, *J*= 246.2 Hz, C-17), 152.01 (s, C-21), 147.38 (s, C-1), 141.91 (d, *J*= 3.1 Hz, C-14), 139.48 (s, C-18), 137.61 (s, C-10), 136.72 (s, C-3), 133.64 (s, C-9), 129.12 (d, *J*= 7.9 Hz, C-15), 128.44 (s, C-12), 127.10 (s, C-13), 126.13 (s, C-11), 124.77 (s, C-8), 122.19 (s, C-2/4), 121.75 (s, C-4/2), 117.14 (s, C-19), 115.60 (d, *J*= 21.2 Hz, C-16), 114.49 (s, C-20), 64.80 (s, C-6), 55.70 (s, C-22), 40.07 (s, C-7);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −115.87

^{15}N-NMR ($CDCl_3$, 60.81 MHz, 295 K): δ [ppm] = 301.9 (m, $N_{pyridine}$), 72.1 (m, *N*H);

MS (HR-DART(+)): m / z 425.2024 ($[M+H]^+$)
calculated: 425.2029 ($C_{28}H_{26}N_2FO \triangleq [M+H]^+$)



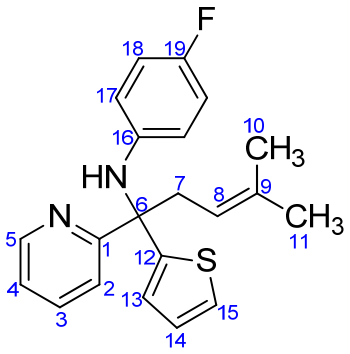
To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.19 mmol, 1 eq) in THF (24 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was stirred for 1 h at room temperature. [Ti(O*i*Pr)$_4$] (1.54 mL, 5.19 mmol, 1 eq) was added and stirring was continued for 10 min. Then, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF and subsequently 1-(bromomethyl)-4-(*tert*-butyl)benzene (3.3 mL, 3.5 eq) were added. The mixture was heated to 60 °C for 18 h and then quenched by the addition of a sat. NH_4Cl solution. Filtration and purification by column chromatography (SiO_2, petrol ether:ethyl acetate = 100:1) gave **6c** as a pale yellow solid (43 %). Single crystals suitable for X-ray diffraction were obtained from a saturated solution of the compound in *n*-hexane at room temperature by slow evaporation of the solvent.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 8.40-8.37 (m, 1H, H-1), 7.66-7.60 (m, 1H, H-3), 7.37 (d, *J*= 8.1 Hz, 1H, H-4), 7.31-7.26 (m, 2H, H-15/16/17), 7.14 (dd, *J*= 7.5 Hz, *J*= 5.1 Hz, 1H, H-2), 7.04 (dd, *J*= 5.1 Hz, *J*= 3.7 Hz, 1H, H-15/16/17), 7.01-6.97 (m, 2H, H-10), 6.84-6.77 (m, 2H, H-20), 6.66-6.38 (m, 3H, N*H* + H-19), 6.34-6.28 (m, 2H, H-9), 4.04 (d, *J*= 13.3 Hz, 1H, H-7), 3.55 (d, *J*= 13.3 Hz, 1H, H-7‘), 1.22 (s, 9H, H-13);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 161.54 (s, C-5), 155.73 (d, *J*= 235.0 Hz, C-21), 151.90 (m, C-14), 149.32 (s, C-11), 146.94 (s, C-1), 141.57 (d, *J*= 1.7 Hz, C-18), 136.74 (s, C-3), 132.47 (s, C-8), 130.07 (s, C-9), 126.84 (s, C-15/16/17), 126.49 (s, C-15/16/17), 124.75 (s, C-15/16/17), 124.58 (s, C-10), 122.12 (s, C-2/4), 122.00 (s, C-2/4), 116.32 (d, *J*= 7.1 Hz, C-19), 115.47 (d, *J*= 22.1 Hz, C-20), 64.42 (s, C-6), 43.60 (s, C-7), 34.43 (s, C-12), 31.45 (s, C-13);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 296 K): δ [ppm] = −128.42 (s, F-21);

MS (HR-DART(+)):	m / z	431.1952	($[M+H]^+$)
	calculated:	431.1957	($C_{27}H_{28}N_2FS$ ≙ $[M+H]^+$)



To a solution of 2-pyridinecarbonitrile (0.5 mL, 5.2 mmol, 1 eq) in THF (20 mL) was added a solution of 2-thienylmagnesium bromide (1 M, 5.2 mL, 1 eq) in THF and the mixture was left stirring for 1 h. Then, [Ti(O*i*Pr)$_4$] (1.54 mL, 5.2 mmol, 1 eq) was added and stirring was continued for 10 min. After that, a solution of 4-fluorophenylmagnesium bromide (1 M, 10.4 mL, 2 eq) in THF was added at room temperature. To this flask was added a solution of the lithium alkoxide of 2-methylbut-3-en-2-ol (5 eq) in THF. The latter was separately prepared from the corresponding allylic alcohol (2.72 mL, 5 eq) and *n*-butyllithium (2.5 M in hexane, 5 eq) in THF (8 mL) at −78 °C followed by warming to room temperature and stirring for 1 h. The reaction mixture was heated to 60 °C for 2 d and then quenched by the addition of sat. NH_4Cl solution. Solid materials were filtered off and the residue was directly purified by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 100:1). **7a** was obtained as a colorless solid (37 %). Single crystals suitable for X-ray diffraction were obtained from a hot solution of the compound in *n*-hexane after slow cooling to −78 °C.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.58 (d, *J*= 4.7 Hz, 1H, H-5), 7.63-7.56 (m, 1H, H-3), 7.30-7.25 (m, 2H, H-2 + $H_{Thiophene}$), 7.24-7.21 (m, 1H, $H_{Thiophene}$), 7.19-7.14 (m, 1H, H-4), 7.02-6.99 (m, 1H, $H_{Thiophene}$), 6.80-6.72 (m, 2H, H-18), 6.52-6.45 (m, 2H, H-17), 4.71-4.64 (m, 1H, H-8), 3.45-3.35 (m, 1H, H-7), 3.08-2.98 (m, 1H, H-7'), 1.50 (s, 3H, H-11), 1.14 (s, 3H, H-10);

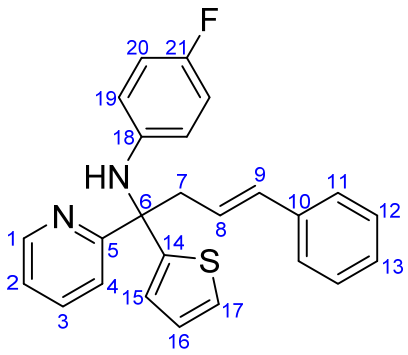
^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 162.26 (s, C-1), 155.89 (d, *J*= 235.5 Hz, C-19), 152.62 (s, C-12), 147.11 (s, C-5), 141.82 (d, *J*= 2.0 Hz, C-16), 136.76 (s, C-3), 135.59 (s, C-9), 126.73 (s, $C_{Thiophene}$), 126.16 (s, $C_{Thiophene}$), 124.23 (s, $C_{Thiophene}$), 121.83 (s, C-4), 121.61 (s, C-2), 117.50 (s, C-8), 116.84 (d, *J*= 7.2 Hz, C-17), 115.17 (d, *J*= 22.0 Hz, C-18), 63.88 (s, C-6), 37.09 (s, C-7), 25.99 (s, C-11), 17.56 (s, C-10

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −127.89 (s);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 300.5 (m, $N_{pyridine}$), 76.7 (m, N*H*);

Elemental analysis:	found:	C 71.58%,	H 5.65%,	N 8.02%,
	calculated:	C 71.56%,	H 6.01%,	N 7.95%.

MS (HR-EI(+)):	m / z	352.1414	($[M]^+$)
	calculated:	352.1409	($C_{21}H_{21}N_2FS$ ≙ $[M]^+$)



To a solution of 2-pyridinecarbonitrile (120 µL, 1.24 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1.24 mL, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(O*i*Pr)$_4$] (368 µL, 1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2.5 mL, 2 eq) in THF. In a second flask, a solution of (*S*)-1-phenyl-2-propen-1-ol (500 mg, 3 eq, enantiopurity: >97:3 e.r.) in THF (5 mL) was cooled to −78 °C and *tert*-butyllithium (1.9 M in pentane, 3.1 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1.5 h. Then, the solution of the lithium alkoxide was added to the reaction mixture and the combined solution was first stirred 4 h at room temperature and then heated to 60 °C for 2 d. Addition of sat. NH_4Cl solution, filtration and purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 40:1) gave **7b** as a colorless foam in 45 % yield (89.9:10.1 e.r.). The product slowly decomposed in $CDCl_3$ solution. Colorless crystals suitable for X-ray diffraction analysis were obtained from a saturated solution of the compound in *n*-hexane at room temperature.

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.64-8.61 (m, 1H, H-1), 7.69 (t, *J*= 7.4 Hz, 1H, H-3), 7.43-7.36 (m, 1H, H-4), 7.34-7.32 (m, 1H, H-15/17), 7.30-7.18 (m, 5H, H-2 + H-12 + H-13 + H-15/17), 7.14-7.11 (m, 2H, H-11), 7.08-7.06 (m, 1H, H-16), 6.84-6.80 (m, 2H, H-20), 6.58-6.54 (m, 2H, H-19), 6.05 (d, *J*= 15.8 Hz, 1H, H-9), 5.76-5.70 (m, 1H, H-8), 3.68 (dd, *J*= 13.9 Hz, *J*= 7.6 Hz, 1H, H-7), 3.23 (dd, *J*= 13.9 Hz, *J*= 7.1 Hz, 1H, H-7‘);

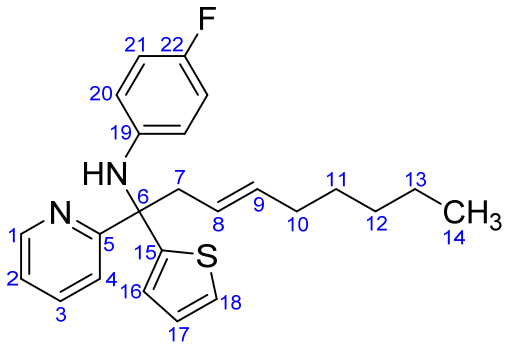
^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 161.79 (s, C-5), 156.24 (d, *J*= 235.8 Hz, C-21), 151.53 (bs, C-14), 147.22 (s, C-1), 141.33 (s, C-18), 137.37 (m, 2C, C-3 + C-10), 134.30 (s, C-9), 128.52 (s, C-12), 127.33 (s, C-13), 126.92 (s, C-16), 126.50 (s, C-15/17), 126.21 (s, C-11), 124.70 (s, C-14), 123.79 (s, C-8), 122.33 (s, C-2), 121.85 (s, C-4), 117.29 (m, C-19), 115.35 (d, *J*= 22.1 Hz, C-20), 64.24 (s, C-6), 42.36 (s, C-7);

$^{19}F\{^{1}H\}$-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −127.49 (s, F-21);

MS (HR-DART(+)): m / z 401.1484 ($[M+H]^+$)
calculated: 401.1488 ($C_{25}H_{21}N_2FS \triangleq [M+H]^+$)

HPLC: Column: AD-H, *n*-hexane:*iso*-propanol = 98:2, λ = 254 nm, flow rate 1 mL/min, 20 °C, $t_{(1)}$= 15.4 min, $t_{(2)}$= 19.7 min. (*S*)-1-Phenyl-2-propen-1-ol yields the product $t_{(1)}$ as major species.

The isolated and characterized (*E*)-isomer was found to be the major product of this reaction and no minor isomeric species could be unambiguously identified in the proton NMR spectrum of the crude product.



To a solution of 2-pyridinecarbonitrile (193 µL, 2.0 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(O*i*Pr)$_4$] (1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF. In a second flask, a solution of 1-octen-3-ol (3 eq) in THF (10 mL) was cooled to −78 °C and *tert*-butyllithium (1.9 M in pentane, 3.1 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then, the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were first stirred 4 h at room temperature and then heated to 60 °C for 2 d. Addition of sat. NH_4Cl solution, filtration and purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 100:1) gave **7c** as a pale yellow solid in 41 % yield. The reaction was also conducted at room temperature for 4 days using chiral (*S*)-1-octen-3-ol (enantiopurity: >99:1 e.r.) to afford the corresponding enantioenriched product (87.7:12.3 e.r.).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 8.61-8.56 (m, 1H, H-1), 7.65-7.58 (m, 1H, H-3), 7.31-7.24 (m, 2H, H-4 + H-16/18), 7.21-7.14 (m, 2H, H-2 + H-16/18), 7.02-6.98 (m, 1H, H-17), 6.80-6.73 (m, 2H, H-21), 6.51-6.45 (m, 2H, H-20), 5.14-5.04 (m, 1H, H-9), 4.97-4.86 (m, 1H, H-8), 3.45-

3.38 (m, 1H, H-7), 3.04-2.95 (m, 1H, H-7'), 1.82-1.73 (m, 2H, H-10), 1.31-1.03 (m, 6H, H-11 + H-12 + H-13), 0.88-0.83 (t, *J*= 7.3 Hz, 3H, H-14);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 162.06 (s, C-5), 155.99 (d, *J*= 235.6 Hz, C-22), 151.88 (s, C-15), 147.16 (s, C-1), 141.51 (m, C-19), 137.00 (s, C-3), 135.77 (s, C-8/9), 126.77 (s, C-17), 126.26 (s, C-16/18), 124.49 (s, C-16/18), 123.14 (s, C-8/9), 122.00 (s, C-2), 121.78 (s, C-4), 116.89 (d, *J*= 7.3 Hz, C-20), 115.25 (d, *J*= 22.1 Hz, C-21), 63.86 (s, C-6), 42.20 (s, C-7), 32.58 (s, C-10), 31.21 (s, C-12), 28.99 (s, C-11), 22.61 (s, C-13), 14.19 (s, C-14);

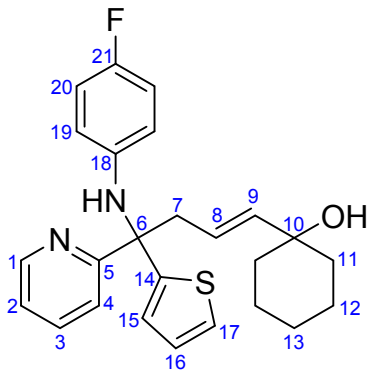
^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −127.84 (s, F-22);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 295 K): δ [ppm] = 299.1 (m, $N_{pyridine}$), 76.7 (m, N*H*);

MS (HR-DART(+)): m / z 395.1953 ($[M+H]^+$)
calculated: 395.1957 ($C_{24}H_{27}N_2FS$ ≙ $[M+H]^+$)

HPLC: Column: AD-H, *n*-hexane:*iso*-propanol = 98:2, λ = 254 nm, flow rate 1 mL/min, 20 °C, $t_{(1)}$= 6.3 min, $t_{(2)}$= 6.8 min. (*S*)-1-Octen-3-ol yields the product $t_{(1)}$ as major species.

The isolated and characterized (*E*)-isomer was found to be the major product of this reaction and no minor isomeric species could be unambiguously identified in the proton NMR spectrum of the crude product.



To a solution of 2-pyridinecarbonitrile (2.0 mmol, 1 eq) in THF (10 mL) at 0 °C was added a solution of 2-thienylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(O*i*Pr)$_4$] (1 eq) was added and, after 10 min, a solution of 4-fluorophenylmagnesium bromide (1 M, 2 eq) in THF. In a second flask, a solution of 1-(propa-1,2-dien-1-yl)cyclohexan-1-ol (see section 2) (3 eq) in THF (10 mL) was cooled to −78 °C and *tert*-butyllithium (1.9 M in pentane, 3.05 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then,

the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were heated to 60 °C for 2 d. Addition of dest. water, filtration and purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 50:1 to 5:1) gave **8a** as a pale brown solid in 41 % yield.

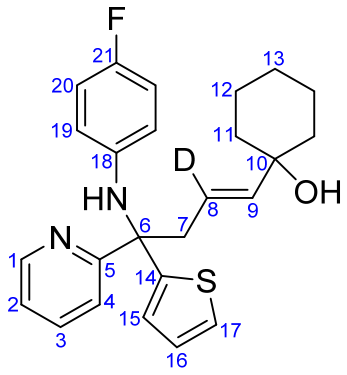
^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.57-8.51 (m, 1H, H-1), 7.61-7.55 (m, 1H, H-3), 7.28-7.23 (m, 2H, H-4 + H-15/17), 7.22 (d, *J*= 3.6 Hz, *J*= 1.0 Hz, 1H, H-15/17), 7.16-7.11 (m, 1H, H-2), 7.00 (dd, *J*= 5.0 Hz, *J*= 3.6 Hz, 1H, H-16), 6.80-6.73 (m, 2H, H-20), 6.56-6.49 (m, 2H, H-19), 5.28-5.15 (m, 2H, H-8 + H-9), 3.56-3.48 (m, 1H, H-7), 3.04-2.97 (m, 1H, H-7'), 1.59-1.15 (m, 10H, H-11 + H-11' + H-12 + H-12' + H-13 + H-13');

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 299 K): δ [ppm] = 161.85 (s, C-5), 155.88 (d, *J*= 235.7 Hz, C-21), 152.08 (s, C-14), 146.91 (s, C-1), 142.22 (s, C-9), 141.45 (d, *J*= 1.8 Hz, C-18), 137.00 (s, C-3), 126.77 (s, C-16), 126.24 (s, C-15/17), 124.24 (s, C-15/17), 121.99 (s, C-2), 121.62 (s, C-4), 120.97 (s, C-8), 116.83 (d, *J*= 7.2 Hz, C-19), 115.17 (d, *J*= 22.1 Hz, C-20), 71.12 (s, C-10), 63.66 (s, C-6), 41.02 (s, C-7), 37.77 (s, C-11), 37.60 (s, C-11'), 25.43 (s, C-13), 22.07 (s, C-12), 22.03 (s, C-12');

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 298 K): δ [ppm] = −127.37 (s, F-21);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 297 K): δ [ppm] = 298.1 (m, $N_{pyridine}$), 76.3 (m, N*H*);

MS (HR-DART(+)):	m / z	423.1926	($[M+H]^+$)
	calculated:	423.1906	($C_{25}H_{29}N_2FOS \triangleq [M+H]^+$)



8a-d_1 was prepared following the same procedure as described for **8a** in a 36 % yield. For the aqueous workup, D_2O was used instead.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.57-8.51 (m, 1H, H-1), 7.61-7.55 (m, 1H, H-3), 7.28-7.23 (m, 2H, H-4 + H-15/17), 7.22 (d, *J*= 3.6 Hz, *J*= 1.0 Hz, 1H, H-15/17), 7.16-7.11 (m, 1H, H-

2), 7.00 (dd, *J*= 5.0 Hz, *J*= 3.6 Hz, 1H, H-16), 6.80-6.73 (m, 2H, H-20), 6.56-6.49 (m, 2H, H-19), 5.17 (1, 1H, H-9), 3.52 (d, *J*= 13.7 Hz, 1H, H-7), 3.00 (d, *J*= 13.7 Hz, 1H, H-7'), 1.59-1.15 (m, 10H, H-11 + H-11' + H-12 + H-12' + H-13 + H-13');

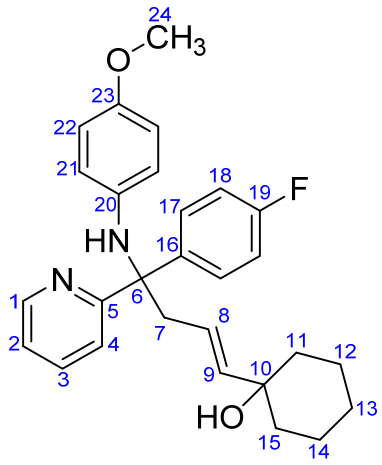
^{2}D{^{1}H}-NMR ($CDCl_3$, 92.12 MHz, 295 K): δ [ppm] = 5.26 (s, D-8);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 299 K): δ [ppm] = 161.85 (s, C-5), 155.88 (d, *J*= 235.7 Hz, C-21), 152.08 (s, C-14), 146.91 (s, C-1), 142.08 (s, C-9), 141.45 (d, *J*= 1.8 Hz, C-18), 137.00 (s, C-3), 126.77 (s, C-16), 126.24 (s, C-15/17), 124.24 (s, C-15/17), 121.99 (s, C-2), 121.62 (s, C-4), 120.75 (t, *J*= 15.1 Hz, C-8), 116.83 (d, *J*= 7.2 Hz, C-19), 115.17 (d, *J*= 22.1 Hz, C-20), 71.20 (s, C-10), 63.60 (s, C-6), 40.87 (s, C-7), 37.77 (s, C-11), 37.60 (s, C-11'), 25.43 (s, C-13), 22.07 (s, C-12), 22.03 (s, C-12');

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 298 K): δ [ppm] = −127.53 (s, F-21);

^{15}N-NMR ($CDCl_3$, 40.52 MHz, 297 K): δ [ppm] = 298.1 (m, $N_{pyridine}$), 76.3 (m, N*H*);

MS (HR-DART(−)):	m / z	422.1822	($[M-H]^-$)
	calculated:	422.1813	($C_{25}H_{25}DN_2FOS$ ≙ $[M-H]^-$)



To a solution of 2-pyridinecarbonitrile (5.2 mmol, 1 eq) in THF (20 mL) at 0 °C was added a solution of 4-fluorophenylmagnesium bromide (1 M, 1 eq) in THF and the mixture was left stirring for 1 h. After that, [Ti(O*i*Pr)$_4$] (1 eq) was added and, after 10 min, a solution of 4-methoxyphenylmagnesium bromide (0.5 M, 2 eq) in THF. In a second flask, a solution of 1-(propa-1,2-dien-1-yl)cyclohexan-1-ol (see section 2) (5 eq) in THF (10 mL) was cooled to −78 °C and *tert*-butyllithium (1.9 M in pentane, 5.25 eq) was added dropwise. The mixture was slowly warmed to room temperature over 1 h. Then,

the solution of the lithium alkoxide was added to the reaction mixture and the combined solutions were heated to 60 °C for 2 d. Addition of dest. water, filtration and purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate:triethylamine = 50:1:1 to 9:1:1) gave **8b** as a yellow oil in 38 % yield.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 297 K): δ [ppm] = 8.56-8.52 (m, 1H, H-1), 7.63-7.49 (m, 3H, H_{Ar} + H-3), 7.13-7.08 (m, 1H, H-2), 7.07-6.99 (m, 3H, H_{Ar} + H-4), 6.66-6.60 (m, 2H, H-21/22), 6.43-6.37 (m, 2H, H-21/22), 6.34 (brs, 1H, N-*H*), 5.34-5.23 (m, 1H, H-8), 5.19-5.12 (m, 1H, H-9), 3.68 (s, 3H, H-24), 3.54-3.44 (m, 1H, H-7), 3.13-3.02 (m, 1H, H-7'), 1.61-1.15 (m, 11H, H_{Alkyl}); The product shows traces of an inseparable impurity.

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 163.13 (s, C-5), 161.82 (d, *J*= 246.1 Hz, C-19), 151.88 (s, C-20/23), 147.08 (s, C-1), 141.97 (d, *J*= 3.1 Hz, C-16), 141.63 (s, C-9), 139.43 (s, C-20/23), 136.67 (s, C-3), 129.07 (d, *J*= 7.9 Hz, C-17), 122.27 (s, C-2/4), 121.91 (s, C-8), 121.65 (s, C-2/4), 116.90 (s, C-21/22), 115.52 (d, *J*= 21.2 Hz, C-18), 114.50 (s, C-21/22), 71.26 (s, C-10), 64.51 (s, C-6), 55.68 (s, C-24), 39.29 (s, C-7), 37.89 (s, C-11/15), 37.67 (s, C-11/15), 25.52 (s, C-13), 22.19 (s, C-12/14), 22.15 (s, C-12/14); The product shows traces of an inseparable impurity.

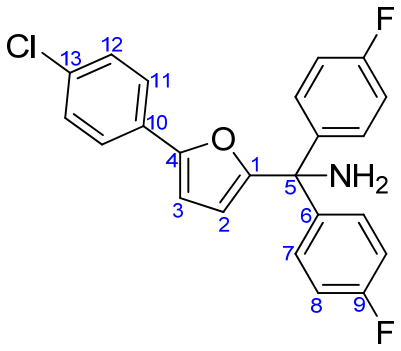
^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −115.87 (s, F-19).

MS (HR-DART(+)):	m / z	447.2443	($[M+H]^+$)
	calculated:	447.2448	($C_{28}H_{32}N_2FO_2$ ≙ $[M+H]^+$)

7. Control reactions

Control reactions were conducted using 5-(4-chlorophenyl)-2-furonitrile and naphthalene-2-carbonitrile. Notably, both reactions yielded solely the trityl amine product.

This reaction was set up in analogy to **GP 1** to elucidate the effect of an O-heterocycle in the vicinity of the nitrile function.



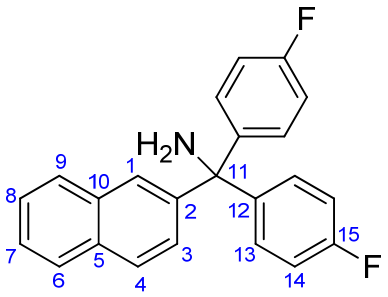
Following **GP 1**, 5-(4-chlorophenyl)-2-furonitrile (1 g, 1 eq), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) tetraisopropoxide (1.45 mL, 1 eq) gave the corresponding trityl amine in 67 % yield after purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 9:1).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 295 K): δ [ppm] = 7.53 (d, *J*= 8.5 Hz, 2H, H-11), 7.36-7.29 (m, 6H, H-7 + H-12), 7.05-6.98 (m, 4H, H-8), 6.58 (d, *J*= 3.3 Hz, 1H, H-3), 6.01 (d, *J*= 3.3 Hz, 1H, H-2), 2.46 (bs, 2H, *N*H_2);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 295 K): δ [ppm] = 161.90 (d, *J*= 246.5 Hz, C-9), 159.40 (s, C-1), 152.74 (s, C-4), 141.87 (d, *J*= 2.9 Hz, C-6), 133.06 (s, C-10/13), 129.14 (d, *J*= 8.0 Hz, C-7), 129.13 (s, C-13/10), 128.89 (s, C-12), 124.91 (s, C-11), 114.93 (d, *J*= 21.3 Hz, C-8), 110.61 (s, C-2), 105.97 (s, C-3), 62.22 (s, C-5);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −115.10 (s);

MS (HR-ESI(+)):	m / z	379.0693	($[M-NH_2]^+$)
	calculated:	379.0696	($C_{23}H_{14}F_2OCl$ ≙ $[M-NH_2]^+$)



Following **GP 1**, 2-naphthonitrile (0.514 g, 1 eq), 4-fluorophenylmagnesium bromide (1 M in THF, 3 eq) and titanium(IV) tetraisopropoxide (2.96 mL, 3 eq) gave the corresponding trityl amine in 86 % yield after purification by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 30:1 to 9:1 + 0.5 % triethylamine).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 7.86-7.78 (m, 2H, H_{Ar}), 7.77-7.72 (m, 1H, H_{Ar}), 7.64-7.62 (m, 1H, H_{Ar}), 7.52-7.44 (m, 2H, H_{Ar}), 7.42-7.37 (m, 1H, H_{Ar}), 7.32-7.25 (m, 4H, H-13), 7.05-6.97 (m, 4H, H-14), 2.40 (bs, 2H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 161.73 (d, *J*= 246.2 Hz, C-15), 145.78 (s, C_{Ar}), 144.11 (d, *J*= 3.2 Hz, C-12), 132.97 (s, C_{Ar}), 132.31 (s, C_{Ar}), 129.92 (d, *J*= 7.9 Hz, C-13), 128.42 (s, $C_{Ar}H$), 127.99 (s, $C_{Ar}H$), 127.55 (s, $C_{Ar}H$), 126.62 (s, $C_{Ar}H$), 126.41 (s, $C_{Ar}H$), 126.34 (s, $C_{Ar}H$), 126.29 (s, $C_{Ar}H$), 114.93 (d, *J*= 21.2 Hz, C-14), 65.71 (s, C-11);

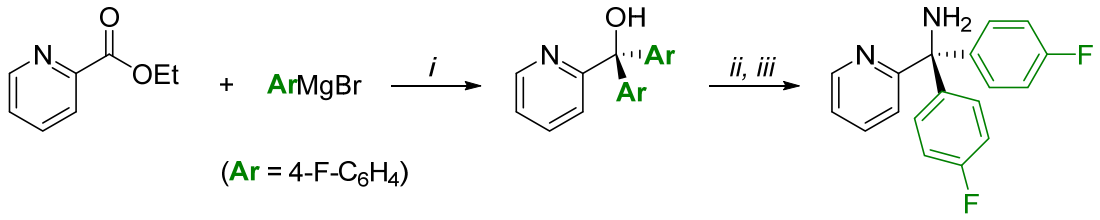
^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −116.01 (s, F-15);

Elemental analysis:	found:	C 79.71%,	H 4.92%,	N 4.25%,
	calculated:	C 79.98%,	H 4.96%,	N 4.06%.

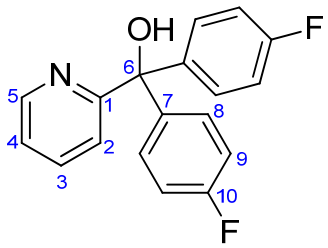
MS (HR-ESI(+)):	m / z	329.1137	($[M-NH_2]^+$)
	calculated:	329.1142	($C_{23}H_{15}F_2 \triangleq [M-NH_2]^+$).

It should be noted, that Gregg *et al.* already employed similar reaction conditions for the preparation of *α*-trisubstituted amines starting from 4-pyridinecarbonitrile or 1-piperidineacetonitrile.[4] These reactions demonstrated that (i) the pyridyl nitrogen has to be directly adjacent to the nitrile function and (ii) a potentially chelating 1,4-diaza motif is not sufficient to ensure azaphilic addition.

In addition, we investigated whether the reaction occurs *via* a tritylamine intermediate which subsequently rearranges to the *N*-aryl species. For this experiment a pyridyl-substituted tritylamine was prepared: starting from ethyl 2-picolinate:



Reaction conditions: (*i*) THF, 0 °C C, rt over night; (*ii*) $SOCl_2$ (excess), *n*-hexane, reflux, 3 h; (*iii*) NH_3 (0.5 M in dioxane, 100 mL), NEt_3 (10 Äq.), CH_3CN, rt, 24 h.



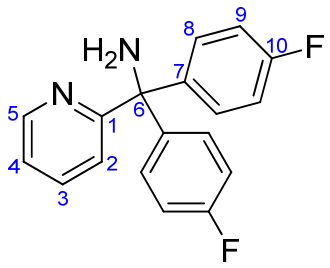
To a solution of 4-fluorophenylmagnesium bromide (0.05 mol, 2.5 eq) in THF (140 mL) at 0 °C a solution of ethyl 2-picolinate (3.02 g, 0.02 mol, 1 eq) in THF (50 mL) was slowly added. The mixture was warmed to room temperature overnight. Then, sat. $NH_4Cl_{(aq)}$ solution was added and the mixture was extracted with Et_2O. The combined organic extracts were dried over anhydrous MgSO4, filtered, evaporated and further purified by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 20:1 to 10:1). The product was obtained as a colorless oil (95 %, 5.63 g).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 8.60-8.56 (m, 1H, H-5), 7.68-7.62 (m, 1H, H-3), 7.28-7.19 (m, 5H, H-4 + H-8), 7.07-7.03 (m, 1H, H-2), 7.01-6.94 (m, 4H, H-9), 6.26 (s, 1H, O*H*);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 296 K): δ [ppm] = 162.94 (s, C-1), 162.20 (d, *J*= 246.6 Hz, C-10), 148.05 (s, C-5), 141.91 (d, *J*= 3.2 Hz, C-7), 136.79 (s, C-3), 129.96 (d, *J*= 8.1 Hz, C-8), 122.76 (m, C-2 + C-4), 114.93 (d, *J*= 21.4 Hz, C-9), 80.19 (s, C-6);

^{19}F-NMR ($CDCl_3$, 188.09 MHz, 295 K): δ [ppm] = −115.10-−115.27 (m, F-10);

MS (HR-ESI(−)):	m / z	296.0890	($[M-H]^-$)
	calculated:	296.0887	($C_{18}H_{12}NF_2O$ ≙ $[M-H]^-$)



To a solution of the alcohol from the previous reaction (5.5 g, 18.5 mmol, 1 eq) in dry *n*-hexane (100 mL) at room temperature was added an excess of $SOCl_2$ (30 mL) and the mixture was stirred for 30 min. Then the reaction mixture was heated to reflux for 3 h, cooled to room temperature and the excess of $SOCl_2$ was removed *in vacuo* to yield a yellow foam. Subsequently, dry CH_3CN (300 mL), dry NEt_3 (25 mL, 10 eq) and a solution of NH_3 in dioxane (0.5 M, 100 mL) was added. The mixture was left stirring at room temperature for 24 h, evaporated to dryness and purified by column chromatography (SiO_2, *n*-pentane:ethyl acetate = 3:1 to dichloromethane:methanol 95:5). The pyridyl-substituted tritylamine was obtained as a brown oil that solidified on standing to give a pale brown solid (1.95 g, 36 %).

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 8.65-8.62 (m, 1H, H-5), 7.61-7.55 (m, 1H, H-3), 7.23-7.15 (m, 5H, H-4 + H-8), 7.03-6.94 (m, 5H, H-2 + H-9), 2.75 (bs, 2H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 165.56 (s, C-1), 161.83 (d, *J*= 246.4 Hz, C-10), 149.24 (s, C-5), 143.52 (d, *J*= 3.2 Hz, C-7), 136.28 (s, C-3), 130.05 (d, *J*= 8.0 Hz, C-8), 122.67 (s, C-2), 121.99 (s, C-4), 114.98 (d, *J*= 21.2 Hz, C-9), 67.01 (s, C-6);

^{19}F-NMR ($CDCl_3$, 188.11 MHz, 295 K): δ [ppm] = −115.87-−116.05 (m, F-10);

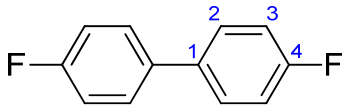
Elemental analysis:	found:	C 73.04%,	H 5.04%,	N 9.39%,
	calculated:	C 72.96%,	H 4.76%,	N 9.45%.

MS (HR-EI(+)):	m / z	296.1137	($[M]^+$)
	calculated:	296.1125	($C_{18}H_{14}N_2F_2$ ≙ $[M]^+$)

However, subjecting this tritylamine product to the reaction conditions showed no signs of conversion. A second indication, that a carbon-to-nitrogen-shift mechanism is not feasible is the observed regioselectivity of the transformation (i.e. no preference for either electron-withdrawing or electron-donating aromatic units).

8. Characterization of byproducts

In the procedures **GP 1** and **GP 2** described above, the second Grignard species is added in excess (generally 2 eq) to obtain higher yields. As a result, small amounts of biphenyl byproducts are formed in less than 10 % yield. To allow identification, the spectroscopic data of two biphenyl compounds is given below.



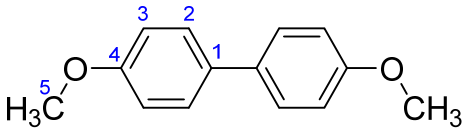
Colorless crystals.

^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 7.51-7.48 (m, 4H, H-2), 7.14-7.10 (m, 4H, H-3);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 162.55 (d, *J*= 246.5 Hz, C-4), 136.53 (d, *J*= 3.3 Hz, C-1), 128.72 (d, *J*= 8.2 Hz, C-2), 115.83 (d, *J*= 21.4 Hz, C-3);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 298 K): δ [ppm] = −115.74 (s);

MS (HR-EI(+)):	m / z	190.0584	($[M]^+$)
	calculated:	190.0594	($C_{12}H_8F_2$ ≙ $[M]^+$)

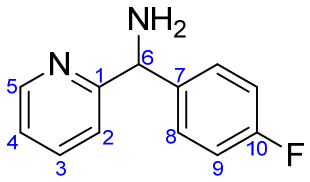


Colorless crystals.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 7.50-7.45 (m, 4H, H-2/3), 6.98-6.93 (m, 4H, H-2/3), 3.84 (s, 6H, H-5);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 158.84 (C_{Ar}), 133.64 (C_{Ar}), 127.88 ($C_{Ar}H$), 114.31 ($C_{Ar}H$),55.50 (C-5);

Other minor byproducts include the mono-arylated primary amines and the corresponding ketones and imines. For each class of compounds a fully characterized example is given below.



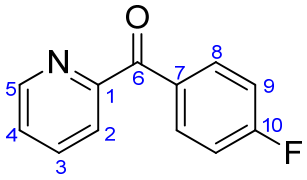
Brown oil.

^{1}H-NMR ($CDCl_3$, 399.89 MHz, 296 K): δ [ppm] = 8.58-8.54 (m, 1H, H-5), 7.63-7.57 (m, 1H, H-3), 7.40-7.34 (m, 2H, H-8), 7.24 (d, *J*= 7.8 Hz, 1H, H-2), 7.16-7.11 (m, 1H, H-4), 7.02-6.95 (m, 2H, H-9), 5.22 (s, 1H, H-6), 2.28 (bs, 2H, *N*H);

^{13}C{^{1}H}-NMR ($CDCl_3$, 100.55 MHz, 298 K): δ [ppm] = 163.29 (s, C-1), 162.06 (d, *J*= 245.7 Hz, C-10), 149.20 (s, C-5), 140.48 (d, *J*= 3.1 Hz, C-7), 136.75 (s, C-3), 128.76 (d, *J*= 8.0 Hz, C-8), 122.17 (s, C-4), 121.56 (s, C-2), 115.45 (d, *J*= 21.4 Hz, C-9), 60.45 (s, C-6);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 297 K): δ [ppm] = −115.64 (s, F-10);

MS (HR-ESI(+)):	m / z	203.0979	($[M+H]^+$)
	calculated:	203.0985	($C_{12}H_{11}N_2F$ ≙ $[M+H]^+$)



Colorless solid.

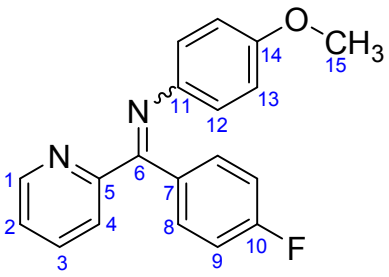
^{1}H-NMR ($CDCl_3$, 600.13 MHz, 295 K): δ [ppm] = 8.72-8.70 (m, 1H, H-5), 8.19-8.14 (m, 2H, H-8), 8.07-8.04 (m, 1H, H-2), 7.93-7.89 (m, 1H, H-3), 7.51-7.48 (m, 1H, H-4), 7.18-7.13 (m, 2H, H-9);

^{13}C{^{1}H}-NMR ($CDCl_3$, 150.90 MHz, 295 K): δ [ppm] = 192.18 (s, C-6), 165.85 (d, *J*= 255.2 Hz, C-10), 155.08 (s, C-1), 148.59 (s, C-5), 137.31 (s, C-3), 133.95 (d, *J*= 9.3 Hz, C-8), 132.66 (d, *J*= 3.0 Hz, C-7), 126.42 (s, C-4), 124.81 (s, C-2), 115.44 (d, *J*= 21.8 Hz, C-9);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −105.25 (s, F-10);

Elemental analysis:	found:	C 71.79%,	H 4.09%,	N 6.95%,
	calculated:	C 71.64%,	H 4.01%,	N 6.96%.

MS (HR-EI(+)):	m / z	201.0600	($[M]^+$)
	calculated:	201.0590	($C_{12}H_8NFO \triangleq [M]^+$)



In solution a mixture of *cis*- and *trans*-isomers of the imine is present. The two isomers (ratio 1 : 0.6) are labeled A and B for the major and minor isomer, respectively.

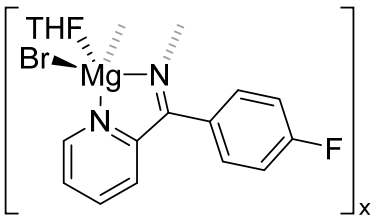
^{1}H-NMR (C_6D_6, 600.13 MHz, 295 K): δ [ppm] = 8.49 (d, *J*= 8.0 Hz, 1H, H_B-1/4), 8.44-8.41 (m, 1H, H_A-1), 8.38-8.34 (m, 1H, H_B-1/4), 7.88-7.83 (m, 2H, H_A-8/9), 7.20-7.16 (m, 1H, H_B-2/3), 7.03-6.98 (m, 2H, H_B-12/13), 6.89-6.84 (m, 2H, H_A-12), 6.82-6.75 (m, 3H, H_A-3 + H_A-8/9), 6.82-6.75 (m, 2H, H_B), 6.69-6.65 (m, 3H, H_B-2/3 + H_B-12/13), 6.64-6.61 (m, 1H, H_A), 6.64-6.61 (m, 2H, H_B-13), 6.60-6.56 (m, 2H, H_A-13), 6.50-6.47 (m, 1H, H_A-2), 3.21(s, 3H, H_B-15), 3.17 (s, 3H, H_A-15);

^{13}C{^{1}H}-NMR (C_6D_6, 150.90 MHz, 295 K): δ [ppm] = 166.13 (s, $C_{B\text{-}Ar}$), 164.79 (s, $C_{A\text{-}Ar}$), 164.73 (d, *J*= 250.9 Hz, C_A-10), 162.82 (d, *J*= 247.6 Hz, C_B-10), 157.92 (s, $C_{B\text{-}Ar}$), 157.02 (s, $C_{B\text{-}Ar}$), 156.81 (s, $C_{A\text{-}Ar}$), 156.36 (s, $C_{A\text{-}Ar}$), 149.62 (s, C_A-1), 148.67 (s, C_B-1), 144.52 (s, $C_{A\text{-}Ar}$), 144.13 (s, $C_{B\text{-}Ar}$), 136.08 (s, $C_{B\text{-}H}$), 135.73 (s, C_A-3), 135.51 (d, *J*= 3.1 Hz, C_A-7), 132.47 (d, *J*= 8.1 Hz, C_B-8‘), 132.27 (d, *J*= 3.6 Hz, C_B-7), 131.64 (d, *J*= 8.6 Hz, C_A-8), 124.50 (s, $C_{A\text{-}H}$), 124.31 (s, $C_{B\text{-}H}$), 123.20 (s, $C_{B\text{-}H}$), 123.10 (s, C_A-12), 123.08 (s, $C_{B\text{-}H}$), 122.84 (s, C_A-2), 115.31 (d, *J*= 21.6 Hz, C_A-9), 114.93 (d, *J*= 21.5 Hz, C_B-9), 114.32 (s, $C_{B\text{-}H}$), 114.19 (s, C_A-13), 54.80 (s, C_B-15), 54.73 (s, C_A-15);

^{19}F{^{1}H}-NMR ($CDCl_3$, 376.27 MHz, 295 K): δ [ppm] = −109.67 (s, F_A), −111.51 (s, F_B);

MS (HR-DART(+)):	m / z	307.1237	($[M+H]^+$)
	calculated:	307.1247	($C_{19}H_{16}N_2FO_2 \triangleq [M+H]^+$) (For [M])

9. Preparation of the homo- and heterometallic reaction intermediates

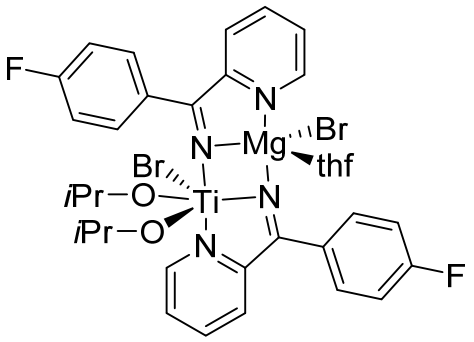


To a solution of 2-pyridinecarbonitrile (0.9 mL, 1 eq) in dry THF (25 mL) at 0 °C was added 4-fluorophenylmagnesium bromide in THF (1 M, 1.05 eq) and the mixture was warmed to room temperature over night. The supernatant was removed by filtration and the residue was washed with THF (2 x 6 mL). Drying *in vacuo* afforded **7** as a bright yellow solid (90 %, 2.55 g). Multinuclear NMR spectra show a multitude of resonances hinting at the presence of a number of metallic species in solution. Single crystals suitable for X-ray diffraction analysis were obtained from a solution of the compound in dichloromethane after layering with toluene and *n*-pentane.

Elemental Analysis: found: C 51.17%, H 4.37%, N 7.55%, calc.: C 51.17%, H 4.29%, N 7.46%. (For [M+THF])

IR (Nujol, KBr, room temperature): relevant region: 1621 cm^{-1}, 1601 cm^{-1}, 1592 cm^{-1}, 1569 cm^{-1}, 1506 cm^{-1}.

MS (LIFDI(+)): m / z 199.4 ([py-ketimide]$^+$)
calc.: 199.1 ($C_{12}H_8N_2F$ ≙ [py-ketimide]$^+$)



To a solution of [TiBr(O*i*Pr)$_3$] (610 mg, 1 eq) in a THF/toluene/*n*-pentane solvent mixture was added the Mg-pyridylketimido complex **7** (751 mg, 1 eq). The mixture was stirred at room temperature for 30 min and filtered through Celite. The clear solution was carefully layered with toluene and *n*-pentane. **8** was obtained as a pale yellow solid (417 mg, 25 %). Multinuclear NMR spectra show a multitude of resonances hinting at the presence of a number of metallic species in solution.

Elemental analysis: found: C 49.36%, H 4.91%, N 7.09%,
calculated: C 49.76%, H 4.67%, N 6.83%.

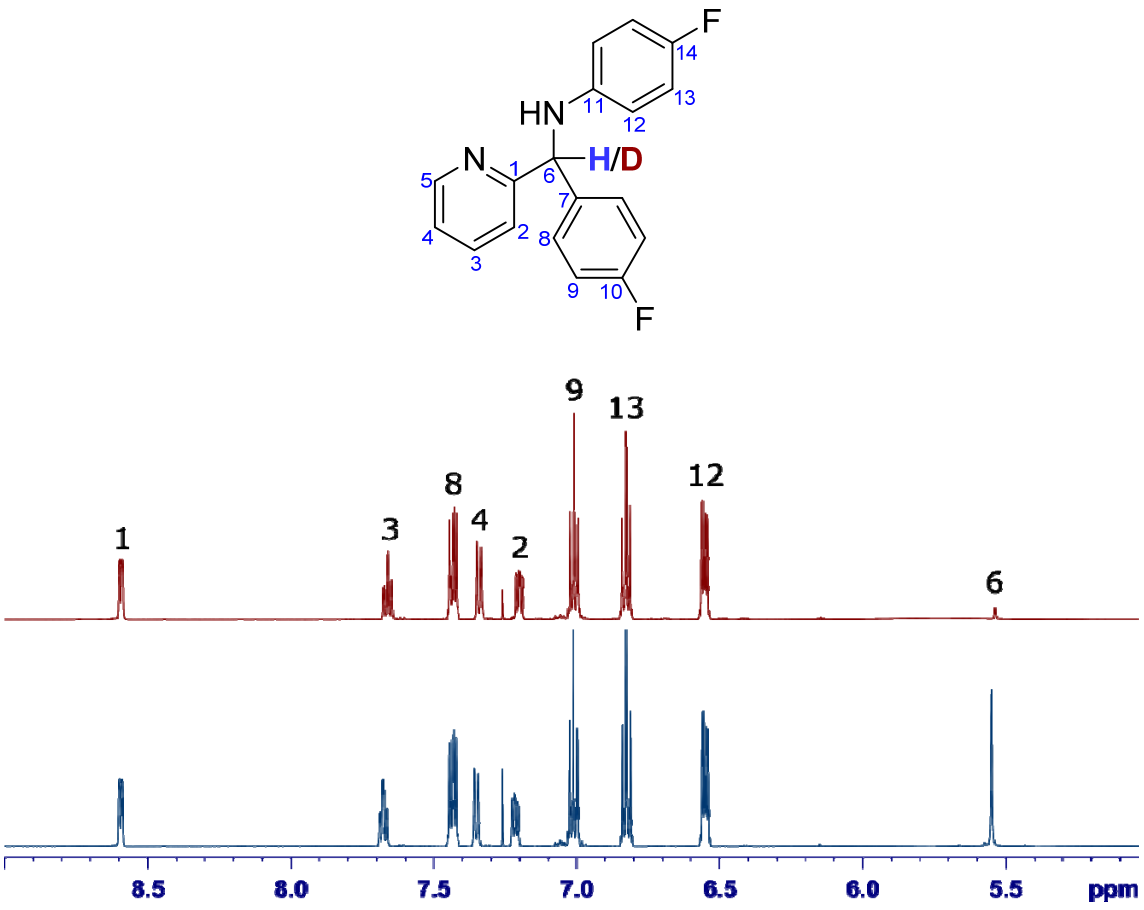
MS (LIFDI(+)): m / z 199.4 ([py-ketimide]$^+$)
calc.: 199.1 ($C_{12}H_8N_2F$ ≙ [py-ketimide]$^+$)

IR (Nujol, KBr, room temperature): relevant region: 1632 cm^{-1}, 1617 cm^{-1}, 1596 cm^{-1}, 1570 cm^{-1}, 1504 cm^{-1}.

For comparison: Reeves *et al.* reported the IR analysis a titanium(IV) ketimine complex which was formed *in situ* from acetophenone, ammonia and [Ti(O*i*Pr)$_4$]. A band at 1626 cm^{-1} was observed and attributed to the C=N bond: J. T. Reeves, Z. Tan, Z. S. Han, G. Li, Y. Zhang, Y. Xu, D. C. Reeves, N. C. Gonnella, S. Ma, H. Lee, B. Z. Lu, C. H. Senanayake, *Angew. Chem.* **2012**, *124*, 1429-1433.

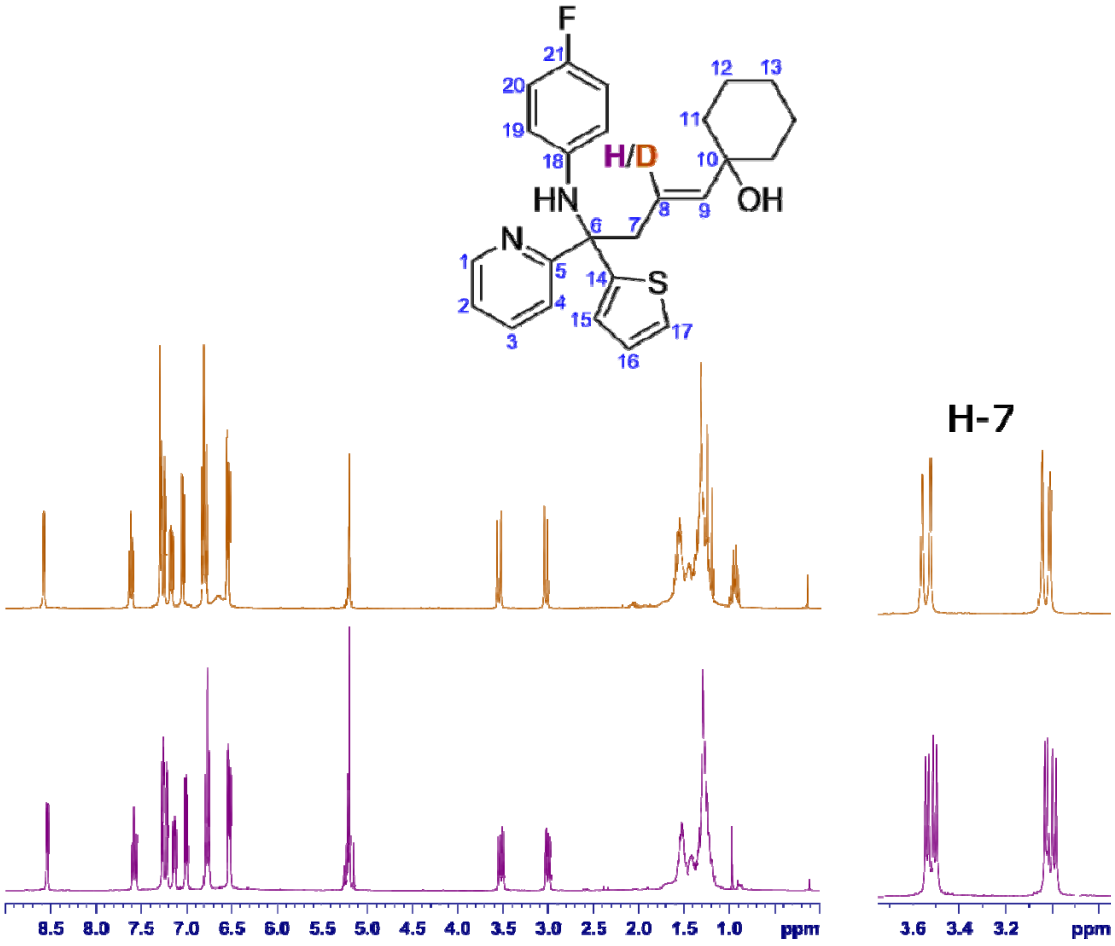
10. Deuteration experiments

In the preparation of benzhydryle amine **1a**-d_1, D_2O was used for quenching the reaction mixture. After column chromatography the dibenzylic position was found to be (almost) quantitatively deuterated (~92 %).



^{1}H NMR spectra of **1a** (bottom) and **1a**-d_1 (top) in $CDCl_3$.

In the preparation of the multicomponent reaction product **8a**-d_1, D_2O was used for quenching the reaction mixture. After column chromatography the vinylic position (H-8) was found to be (almost) quantitatively deuterated (~94 %). In the ^{1}H-NMR spectra the deuteration has a pronounced effect on the H-7 protons (shown on the right).



Left: ^{1}H NMR spectra of **8a** (bottom) and **8a**-d_1 (top) in $CDCl_3$. Right: Section of the ^{1}H NMR spectra displaying the coupling pattern of H-7 in **8a** and **8a**-d_1.

11. X-ray Crystal Structure Determinations

Crystal data and details of the structure determinations are compiled in Tables **S1-S2**. Full shells of intensity data were collected at low temperature with a Bruker AXS Smart 1000 CCD diffractometer (Mo-K_a radiation, sealed X-ray tube, graphite monochromator; compounds **2i**, **6c**, **7a** and **7b**) or a Agilent Technologies Supernova-E CCD diffractometer (Mo- or Cu-K_a radiation, microfocus X-ray tube, multilayer mirror optics; all other compounds). Data were corrected for air and detector absorption, Lorentz and polarization effects;[5,6] absorption by the crystal was treated analytically,[6,7] numerically (Gaussian grid)[6,8] or with a semiempirical multiscan method.[9,10,11]

The structures were solved by direct methods with dual-space recycling (compound **7b**),[12] by intrinsic phasing (compound **3**)[13] or by the charge flip procedure (all other compounds)[14] and refined by full-matrix least squares methods based on F^2 against all unique reflections.[15] All non-hydrogen atoms were given anisotropic displacement parameters. Hydrogen atoms were generally input at calculated positions and refined with a riding model. When justified by the quality of the data the positions of some hydrogen atoms were taken from difference Fourier syntheses and refined. When found necessary, disordered groups where subjected to suitable geometry and adp restraints. Due to severe disorder and fractional occupancy, some electron density attributed to solvent (dichloromethane) of crystallization was removed from the structures of **3** with the BYPASS procedure,[16] as implemented in PLATON (SQUEEZE).[17] Partial structure factors from the solvent masks were included in the refinement as separate contributions to F_{obs}.

Supporting Information Available: CIF files giving crystallographic data for compounds **1c**, **1e**, **2i**, **3**, **4**, **5a**, **6c**, **7a**, **7b**, **8a**.

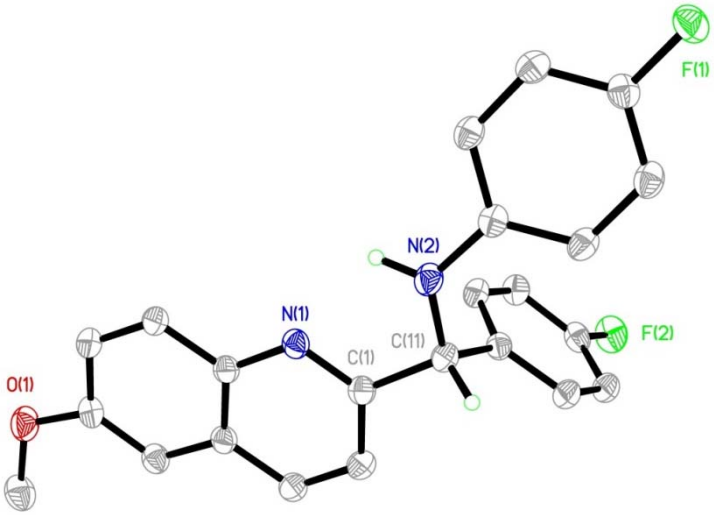
Table S1. Details of the crystal structure determinations.

	1c	**1e**	**2i**	**3**	**4**
formula	$C_{16}H_{13}FN_2S$	$C_{23}H_{18}F_2N_2O$	$C_{17}H_{14}F_2N_2S$	$C_{100}H_{72}Br_8Cl_8F_8Mg_8N_{16}$	$C_{34}H_{38}Br_2F_2MgN_4O_3Ti$
M_r	284.34	376.39	316.36	2767.09	820.71
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	triclinic
space group	$P\,2_1/n$	$C\,2/c$	$P\,2_1/c$	$P\,2_1/c$	P -1
a /Å	10.195(4)	15.7539(3)	18.0092(2)	22.4267(3)	9.8718(3)
b /Å	9.490(4)	9.65061(16)	10.00543(13)	16.2143(2)	10.4703(4)
c /Å	13.914(7)	24.0594(4)	17.4500(3)	32.7617(5)	17.5861(5)
α /°					97.588(3)
β /°	91.837(11)	98.5049(17)	97.0396(13)	101.0556(14)	94.438(2)
γ /°					95.282(3)
V /Å^3	1345.6(10)	3617.63(11)	3120.61(8)	11692.1(3)	1786.75(10)
Z	4	8	8	4	2
F_{000}	592	1568	1312	5472	832
d_c /Mg·m^{-3}	1.404	1.382	1.347	1.572	1.525
X-radiation, λ /Å	Mo-K_α, 0.71073	Mo-K_α, 0.71073	Cu-K_α, 1.5418	Mo-K_α, 0.71073	Mo-K_α, 0.71073
μ /mm^{-1}	0.242	0.100	2.012	3.033	2.543
max., min. transmission factors	0.8623, 0.8209	1.0000, 0.9394	0.935, 0.728	0.835, 0.547	0.852, 0.687
data collect. temperat. /K	100(2)	110(1)	110(2)	120(1)	120(1)
θ range /°	2.4 to 32.5	3.3 to 32.6	4.9 to 70.8	3.2 to 27.1	3.3 to 28.7
index ranges h,k,l	-14 ... 14, -14 ... 14, -20 ... 20	-23 ... 23, -14 ... 14, -36 ... 36	-21 ... 21, -12 ... 12, -20 ... 21	-28 ... 28, -20 ... 20, -41 ... 41	-13 ... 13, -14 ... 14, -23 ... 23
reflections measured	33321	68525	66994	202860	39199
unique [R_{int}]	4627 [0.0449]	6575 [0.0789]	5972 [0.0512]	25754 [0.0792]	9238 [0.0662]
observed [$I \geq 2\sigma(I)$]	3685	4573	4963	19620	6606
parameters refined	221	301	467	1343	428
GooF on F^2	1.044	1.047	1.013	1.036	1.041
R indices [$F>4\sigma(F)$] $R(F)$, $wR(F^2)$	0.0443, 0.1060	0.0505, 0.1179	0.0337, 0.0852	0.0590, 0.1277	0.0519, 0.1151
R indices (all data) $R(F)$, $wR(F^2)$	0.0604, 0.1172	0.0804, 0.1327	0.0439, 0.0914	0.0840, 0.1385	0.0827, 0.1294
Difference density: max, min /e·Å^{-3}	0.551, -0.264	0.357, -0.230 [3]	0.267, -0.202	2.113, -1.780	1.553, -0.464

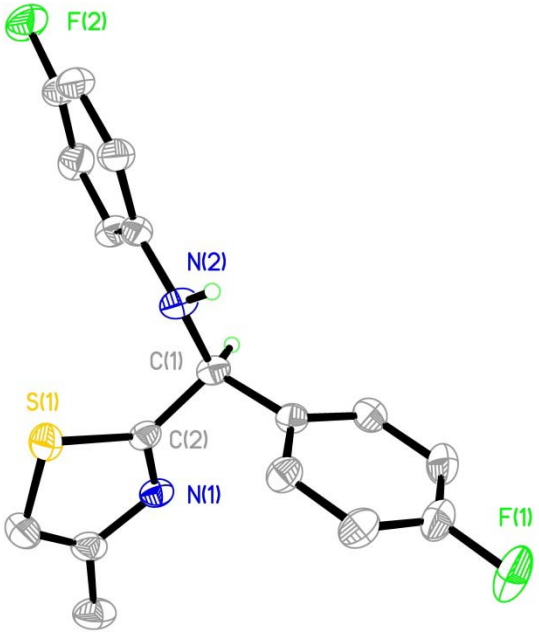
Table S2. Details of the crystal structure determinations.

	5a	**6c**	**7a**	**7b**	**8a**
formula	$C_{20}H_{18}FN_3O_2$	$C_{27}H_{27}FN_2S$	$C_{21}H_{21}FN_2S$	$C_{25}H_{21}FN_2S$	$C_{25}H_{27}FN_2OS$
M_r	351.37	430.56	352.46	400.50	422.54
crystal system	monoclinic	triclinic	monoclinic	triclinic	triclinic
space group	*C* 2/*c*	*P* -1	*P* $2_1/n$	*P* -1	*P* -1
a /Å	20.5079(8)	10.526(5)	12.052(6)	8.573(3)	10.25396(16)
b /Å	7.57317(19)	11.253(5)	11.172(5)	11.492(4)	13.4798(2)
c /Å	23.5113(8)	11.792(6)	13.492(7)	11.507(5)	16.1777(3)
α /°		96.617(15)		76.707(13)	91.6383(14)
β /°	113.312(4)	113.902(11)	98.667(10)	77.201(6)	100.6718(13)
γ /°		109.266(16)		68.963(8)	94.9664(14)
V /Å^3	3353.4(2)	1154.3(10)	1795.9(16)	1017.6(7)	2186.89(6)
Z	8	2	4	2	4
F_{000}	1472	456	744	420	896
d_c /Mg·m^{-3}	1.392	1.239	1.304	1.307	1.283
X-radiation, *λ* /Å	Cu-K_α, 1.5418	Mo-K_α, 0.71073	Mo-K_α, 0.71073	Mo-K_α, 0.71073	Mo-K_α, 0.71073
μ /mm^{-1}	0.819	0.165	0.195	0.181	0.176
max., min. transmission factors	0.930, 0.873	0.8623, 0.8137	0.7462, 0.6722	0.8623, 0.8031	0.991, 0.968
data collect. temperat. /K	110(1)	100(1)	100(2)	100(1)	120(1)
θ range /°	4.1 to 70.4	2.0 to 30.5	2.1 to 31.1	1.8 to 32.5	3.3 to 28.9
index ranges *h*,*k*,*l*	-21 ... 24, -9 ... 9, -28 ... 28	-15 ... 15, -16 ... 16, -16 ... 16	-17 ... 17, -16 ... 16, -19 ... 19	-12 ... 12, -17 ... 17, -17 ... 17	-13 ... 13, -17 ... 18, -21 ... 21
reflections measured	38825	28265	44346	26274	62602
unique [R_{int}]	3161 [0.0886]	7025 [0.0329]	5760 [0.0587]	6868 [0.0235]	10753 [0.0459]
observed [$I \geq 2\sigma(I)$]	2824	5164	4304	5965	9252
parameters refined	282	318	266	326	558
GooF on F^2	1.115	1.026	1.057	1.055	1.137
R indices [$F>4\sigma(F)$] $R(F)$, $wR(F^2)$	0.0421, 0.0902	0.0699, 0.1895	0.0450, 0.1106	0.0457, 0.1225	0.0688, 0.1575
R indices (all data) $R(F)$, $wR(F^2)$	0.0502, 0.0942	0.0932, 0.2096	0.0683, 0.1240	0.0526, 0.1291	0.0808, 0.1633
Difference density: max, min /e·Å^{-3}	0.194, -0.184	1.037, -0.395	0.547, -0.305	0.754, -0.313	0.591, -0.743

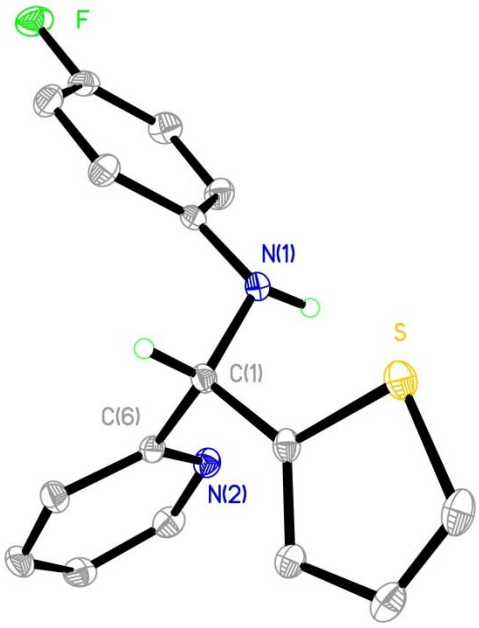
12. Solid State Structures



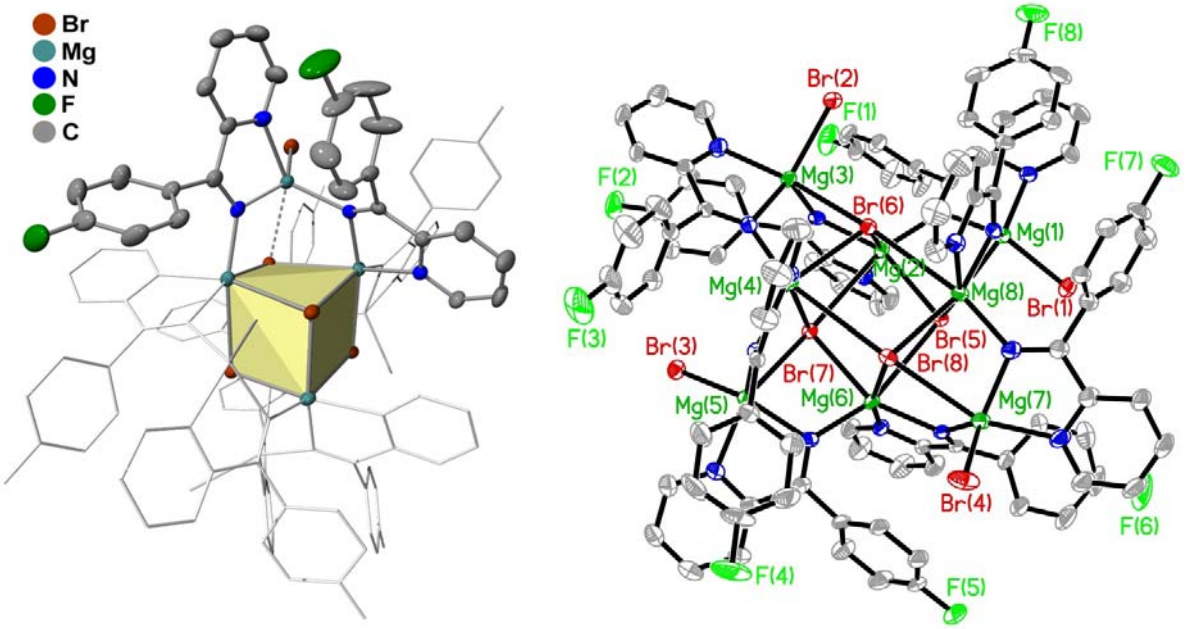
Molecular structure of compound **1c**, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(2)-*H* and the benzylic C(11)-*H*, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.3150(16), C(1)-C(11) 1.5274(18), C(11)-N(2) 1.4456(16), N(1)-C(1)-C(11)-N(2) 8.40(16).



Molecular structure of compound **1e**, thermal ellipsoids set at the 50 % probability level. The other enantiomer and H-atoms, except N(2)-*H* and the benzylic C(1)-*H*, have been omitted for clarity. Selected bond lengths [Å] and angles [°] (values in square brackets refer to the second independent molecule): N(1)-C(2) 1.3019(19) [1.3026(19)], C(1)-C(2) 1.513(2) [1.516(2)], C(1)-N(2) 1.4516(19) [1.4540(18)], N(1)-C(2)-C(1)-N(2) 174.04(13) [-167.30(13)].

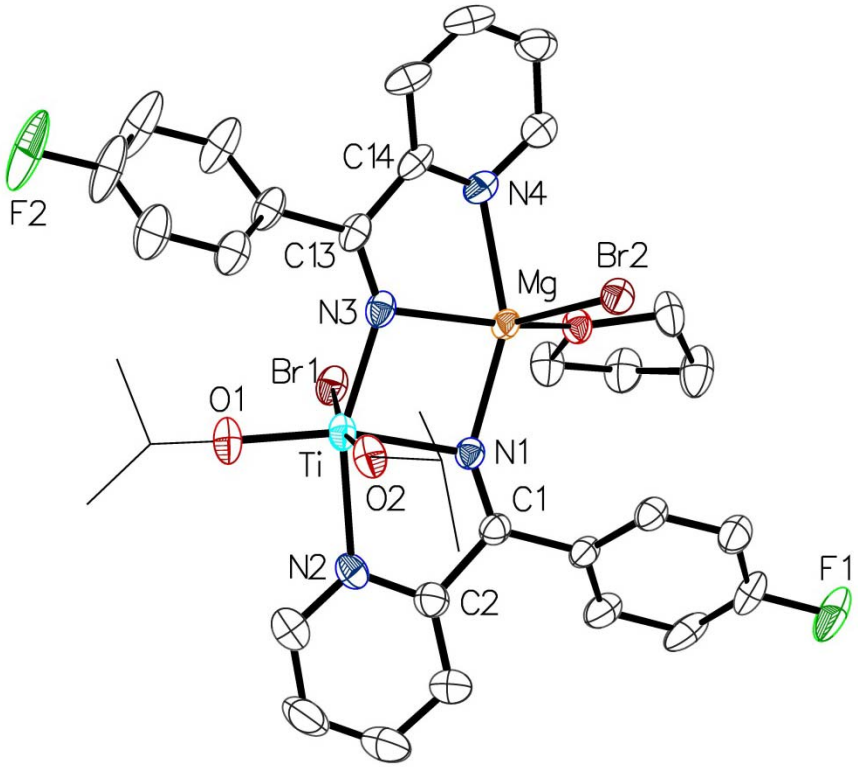


Molecular structure of compound **2i**, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-*H* and the benzylic C(1)-*H*, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4659(16), C(1)-C(6) 1.5259(17), C(6)-N(2) 1.3426(17), N(1)-C(1)-C(6)-N(2) 40.78(14).



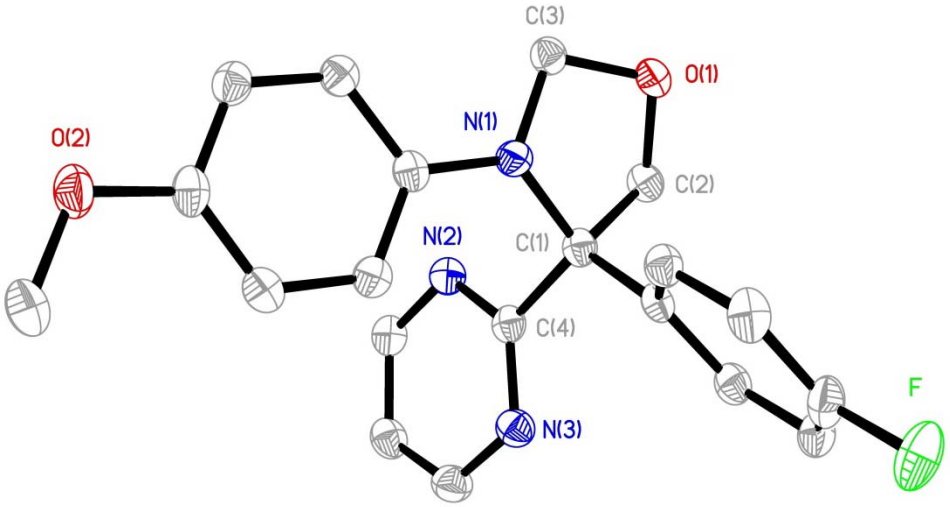
Molecular structure of compound **3**, thermal ellipsoids set at the 50 % probability level. H-atoms and cocrystallized solvent molecules have been omitted for clarity. Left: The central Mg_4Br_4 cube has been colored for emphasis. Selected avg. bond lengths [Å] and angles [°]: N_{Py}-Mg 2.163±0.007, N_{Imide}-Mg (chelat) 2.098±0.009, N_{Imide}-Mg (bridging) 2.055±0.010, C-N_{Imide} 1.263±0.004, C_{Py}-C_{Imide}

1.514±0.005, Mg···Mg 3.494±0.021, Mg-Br (terminal) 2.514±0.020, N_{Py}-Mg-N_{Imide} 79.31±0.36, Mg_{Imide}-N-Mg_{Imide} 114.57±0.91.

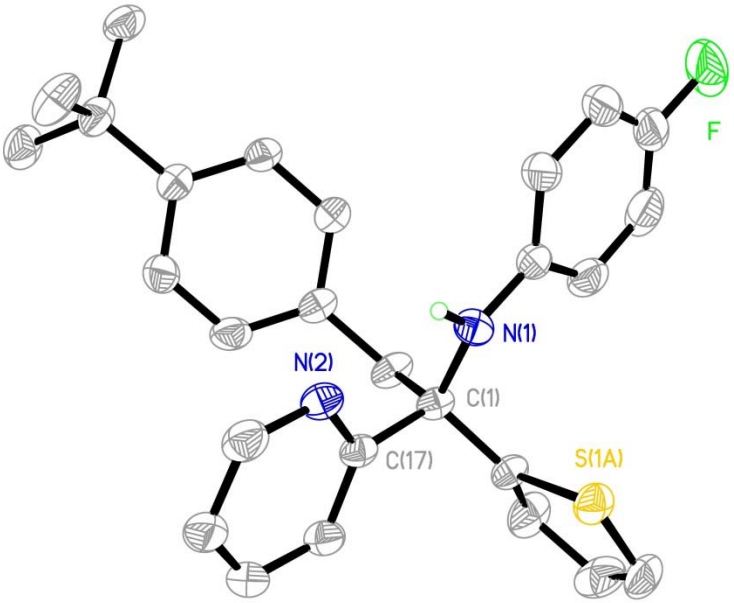


Molecular structure of compound **4**, thermal ellipsoids set at the 50 % probability level. H-atoms have been omitted for clarity, *iso*-propyl groups are drawn as wireframes. Selected bond lengths [Å] and angles [°]: Br(1)-Ti 2.6938(8), Br(2)-Mg 2.5448(13), Ti-Mg 3.1656(13), Ti-O(1) 1.808(3), Ti-O(2) 1.798(3), Ti-N(1) 2.140(3), Ti-N(2) 2.245(3), Ti-N(3) 2.028(3), Mg-O(3) 2.073(3), Mg-N(1) 2.102(3), Mg-N(3) 2.163(3), Mg-N(4) 2.192(3), N(1)-C(1) 1.277(4), N(2)-C(2) 1.350(5), N(3)-C(13) 1.275(5), N(4)-C(14) 1.348(5), C(1)-C(2) 1.502(5), C(13)-C(14) 1.506(6), Br(1)-Ti-Mg 71.23(3), O(1)-Ti-Br(1) 88.53(9), O(1)-Ti-Mg 148.58(10), O(1)-Ti-N(1) 158.19(12), O(1)-Ti-N(2) 89.95(13), O(1)-Ti-N(3) 111.61(13), O(2)-Ti-Br(1) 168.89(9), O(2)-Ti-Mg 97.92(9), O(2)-Ti-O(1) 102.34(13), O(2)-Ti-N(1) 91.68(12), O(2)-Ti-N(2) 89.41(12), O(2)-Ti-N(3) 94.14(13), N(1)-Ti-Br(1) 78.62(8), N(1)-Ti-N(2) 73.38(11), N(2)-Ti-Br(1) 92.92(8), N(3)-Ti-Br(1) 79.52(9), N(3)-Ti-N(1) 83.52(11), N(3)-Ti-N(2) 156.73(12), Br(2)-Mg-Ti 119.34(4), O(THF)-Mg-Br(2) 102.56(8), O(THF)-Mg-Ti 129.03(8), N(1)-Mg-Br(2) 108.96(9), N(1)-Mg-N(3) 81.25(12), N(1)-Mg-N(4) 154.08(13), N(3)-Mg-Br(2) 109.14(9), N(3)-Mg-N(4) 75.83(12), N(4)-Mg-Br(2) 90.08(9), Mg-N(1)-Ti 96.52(12), C(1)-N(1)-Ti 119.7(2), C(1)-N(1)-Mg 143.6(3), C(2)-N(2)-Ti 115.3(2), Ti-N(3)-Mg 98.08(13), C(13)-N(3)-Ti 144.1(3), C(13)-N(3)-Mg 115.9(3), C(14)-N(4)-Mg 112.7(2), N(1)-C(1)-C(2) 117.4(3), N(2)-C(2)-C(1) 112.9(3), Ti-N(1)-C(1)-C(2) 1.1(4), Ti-N(2)-C(2)-C(1) -12.5(4), Mg-N(1)-C(1)-C(2) -173.5(3), Mg-

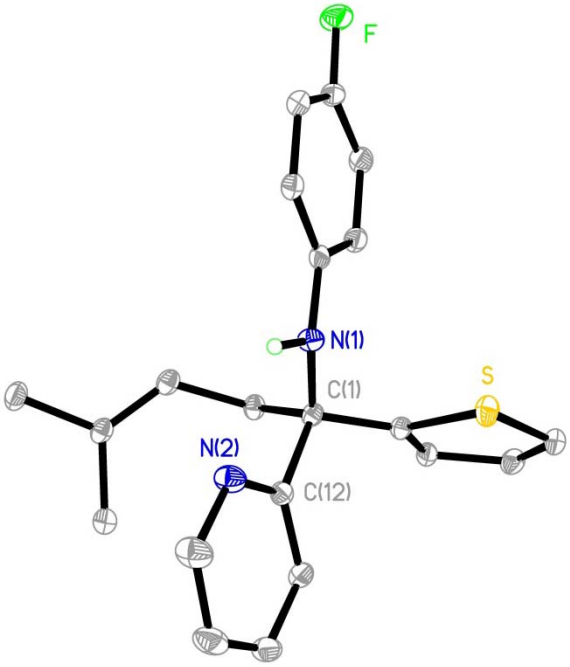
N(3)-C(13)-C(14) -3.1(4), Mg-N(4)-C(14)-C(13) -21.6(4), N(1)-C(1)-C(2)-N(2) 7.9(5), N(3)-C(13)-C(14)-N(4) 17.1(5).



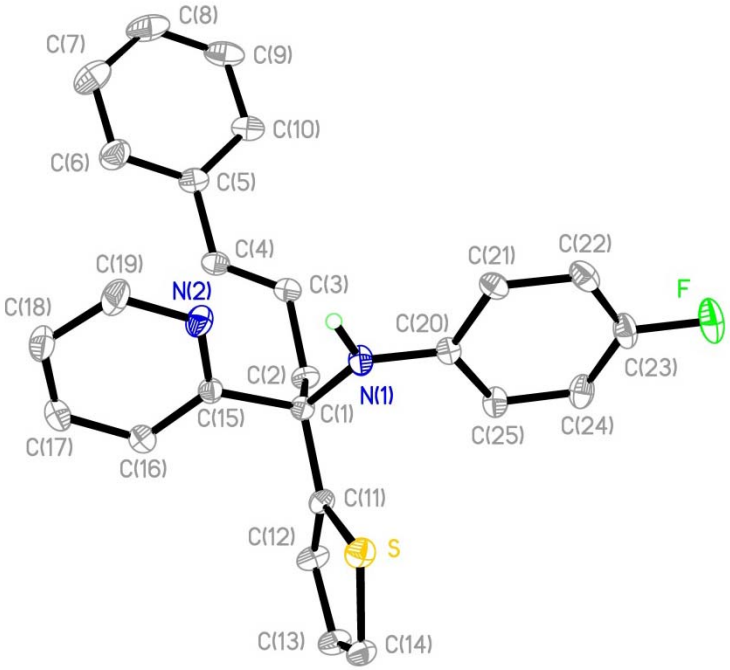
Molecular structure of compound **5a**, thermal ellipsoids set at the 50 % probability level. H-atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(2)-C(4) 1.341(2), C(1)-C(4) 1.538(2), C(1)-N(1) 1.4637(19), N(2)-C(4)-C(1)-N(1) 50.15(17), N(1)-C(1)-C(2)-O(1) 27.84(15).



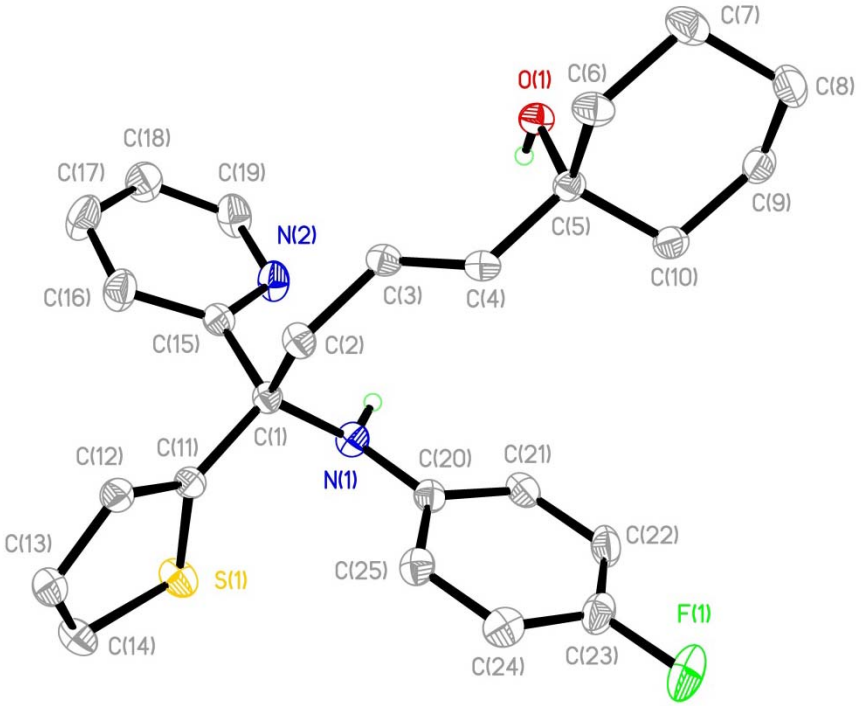
Molecular structure of compound **6c**, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-*H*, and the disorder within the *tert*-butyl group have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.459(2), C(1)-C(17) 1.536(3), N(2)-C(17) 1.333(2), N(1)-C(1)-C(17)-N(2) 17.87(19).



Molecular structure of compound **7a**, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-*H*, have been omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4615(18), C(1)-C(12) 1.542(2), C(12)-N(2) 1.3378(19), N(1)-C(1)-C(12)-N(2) 23.22(16).



Molecular structure of compound **7b**, thermal ellipsoids set at the 50 % probability level. H-atoms, except N(1)-*H*, are omitted for clarity. Selected bond lengths [Å] and angles [°]: N(1)-C(1) 1.4517(14), C(1)-C(2) 1.5614(16), C(1)-C(11) 1.5152(15), C(1)-C(15) 1.5431(15), C(3)-C(4) 1.3322(16), N(1)-C(1)-C(15)-N(2) 17.72(12).



Molecular structure of compound **8a**, thermal ellipsoids set at the 50 % probability level. H-atoms, except O(1)-*H* and N(1)-*H*, have been omitted for clarity. Only one of the two independent molecules is shown. Selected bond lengths [Å] and angles [°] (values in square bracket refer to the second independent molecule): O(1)-C(5) 1.439(3) [1.444(3)], N(1)-C(1) 1.464(3) [1.483(3)], N(2)-C(15) 1.339(3), C(1)-C(15) 1.546(3) [1.546)], C(2)-C(3) 1.498(3) [1.501(3)], C(3)-C(4) 1.321(3) [1.324(3)], C(4)-C(5) 1.512(3) [1.512(3)], C(1)-C(11) 1.525(3) [1.524(3)], N(1)-C(20) 1.402(3) [1.410(3)], C(20)-N(1)-C(1) 122.76(19) [121.5(2)], N(1)-C(1)-C(2) 113.16(18) [112.16(19)], N(1)-C(1)-C(11) 109.53(18) [111.1(2)], N(1)-C(1)-C(15) 108.40(18) [106.40(19)], C(11)-C(1)-C(2) 108.77(18) [108.63(19)], C(11)-C(1)-C(15) 109.71(18) [107.04(19)], C(15)-C(1)-C(2) 107.22(18) [111.4(2)], C(3)-C(2)-C(1) 113.68(18)]112.68(19)], C(4)-C(3)-C(2) 123.5(2) [124.7(2)], C(3)-C(4)-C(5) 125.8(2) [125.6(2)], O(1)-C(5)-C(4) 111.00(18) [110.75(18)], N(1)-C(1)-C(15)-N(2) -23.7(3), C(3)-C(4)-C(5)-O(1) -13.3(3) [13.2(3)].

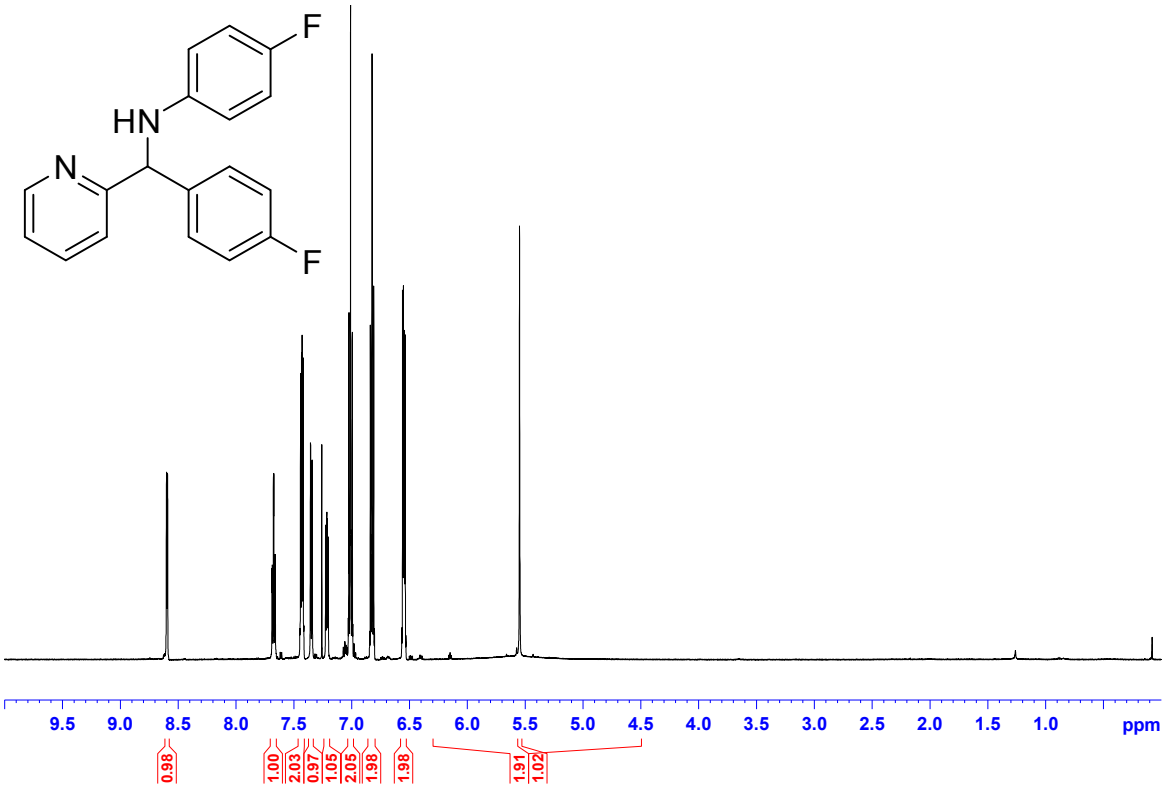
13. Computational Details

Geometry optimizations have been performed with the Gaussian09 package[18] at the PBE0 level of hybrid density functional theory.[19] The atoms (Ti, C, H, N, O, Br, Mg) were represented by a svp basis set.[20] The solvent (thf) influence was taken into consideration through single point calculations on the gas-phase optimized geometry with SCRF calculations within the SMD model.[21] For the SCRF calculations the atoms were treated with a tzvp basis set.[22] All energies reported in the present work are Gibbs free energies obtained by summing the SMD energy and the gas-phase Gibbs contribution at 333 K (see Table below for the corresponding values in atomic units). The NBO analysis were carried out, using NBO 6.0,[23] on wavefunctions computed with PBE0 in gas phase with a tzvp basis set for all the atoms.

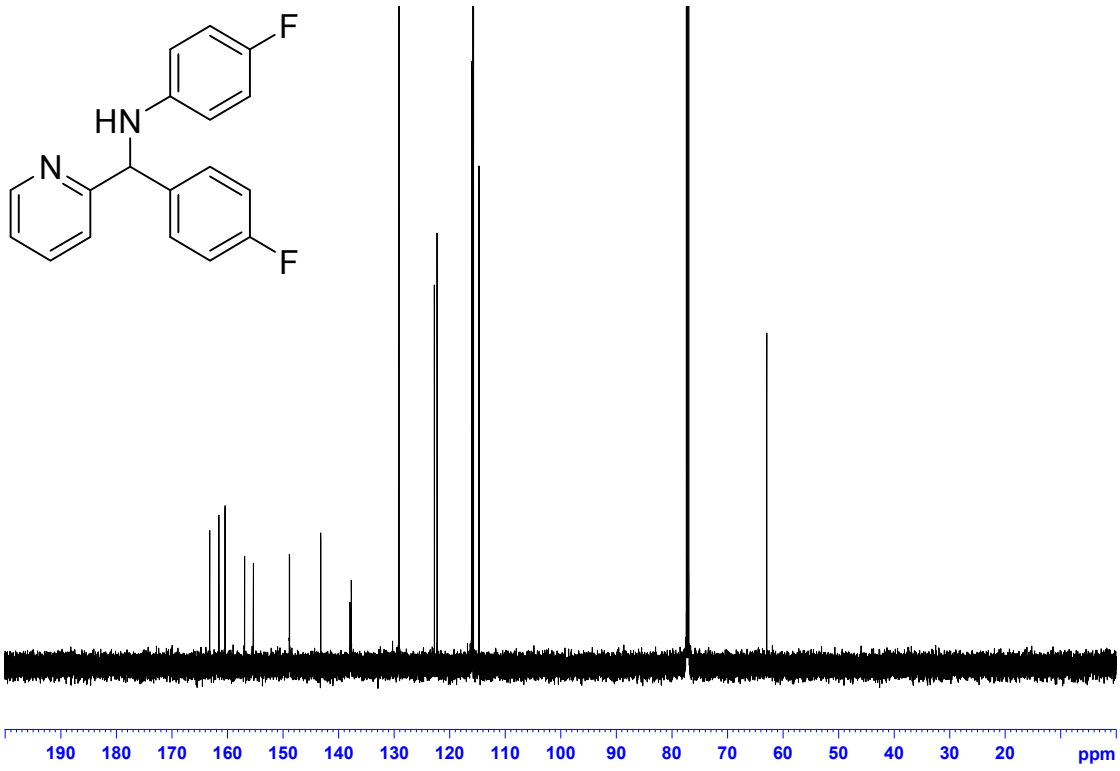
	E(smd/tzvp)	G(333 K)
A-cyc	-4970,068903	0,304339
TS-A-C-cyc	-4970,06041	0,303527
C-cyc	-4970,066043	0,305864
TS-C-D-cyc	-4970,032508	0,305857
D-cyc	-4970,086525	0,305461
TS-A-B-cyc	-4970,023162	0,307102
B-cyc	-4970,094863	0,304412
A	-4970,042019	0,297799
TS-A-C	-4970,031993	0,30192
C	-4970,036047	0,302822
TS-C-D	-4970,002343	0,302217
D	-4970,06148	0,309079
TS-A-B	-4970,003427	0,300543
B	-4970,067191	0,302399
E-cyc	-4970,099608	0,306302
Mg(Br)(Ar)	-3104,545986	0,041257
Ti-solo-cyc	-1865,466189	0,234209
Ti-solo	-1865,45455	0,227282

14. NMR Spectra

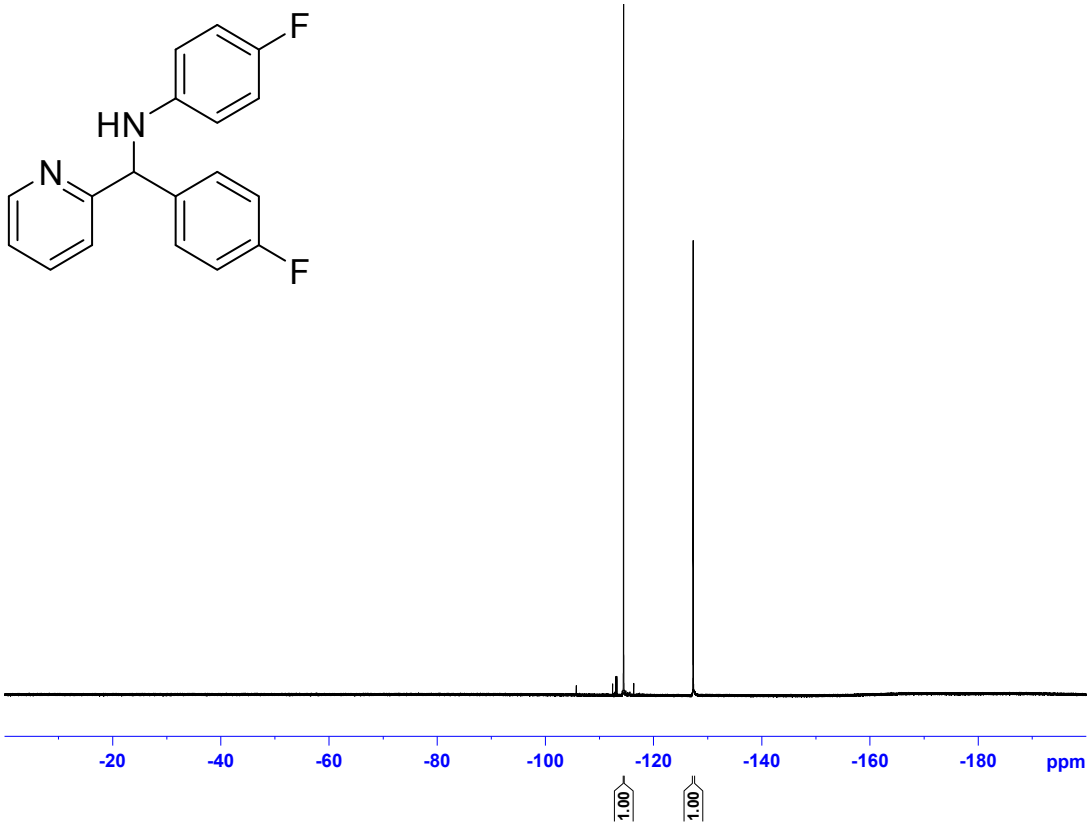
1a (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



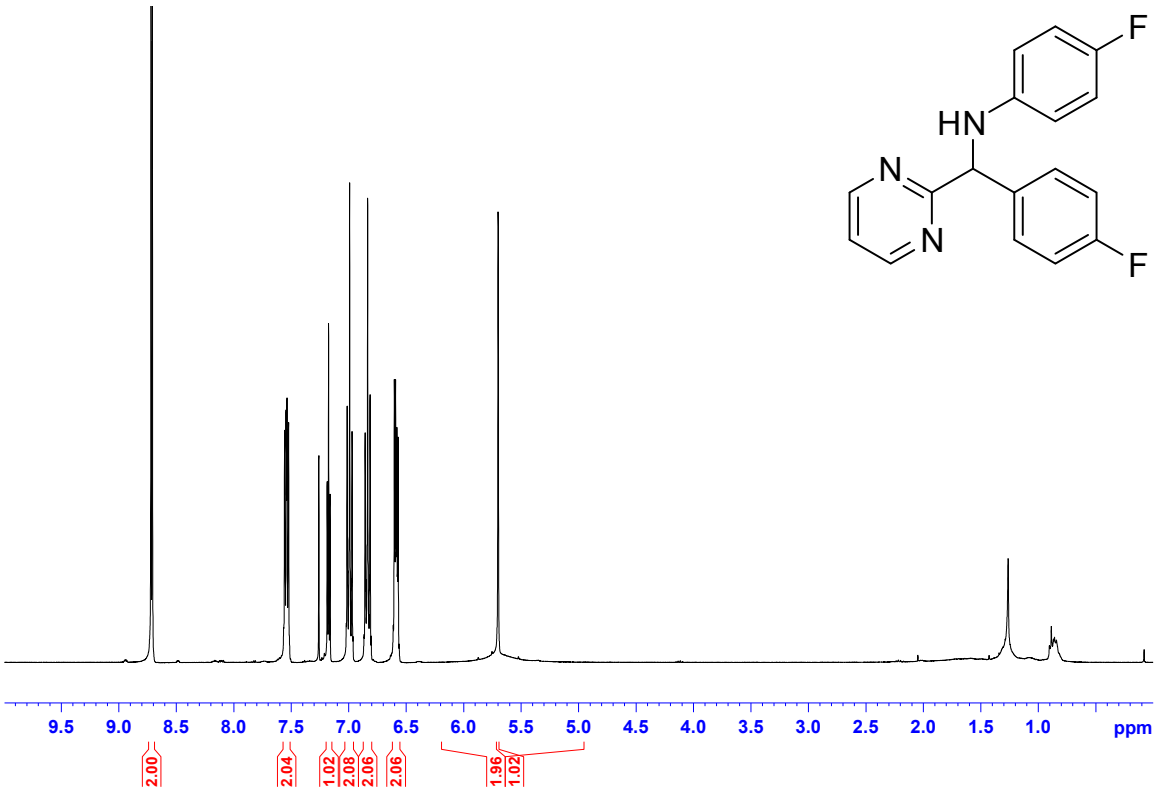
1a (^{13}C{^{1}H} NMR, $CDCl_3$, 150.90 MHz, 296 K)



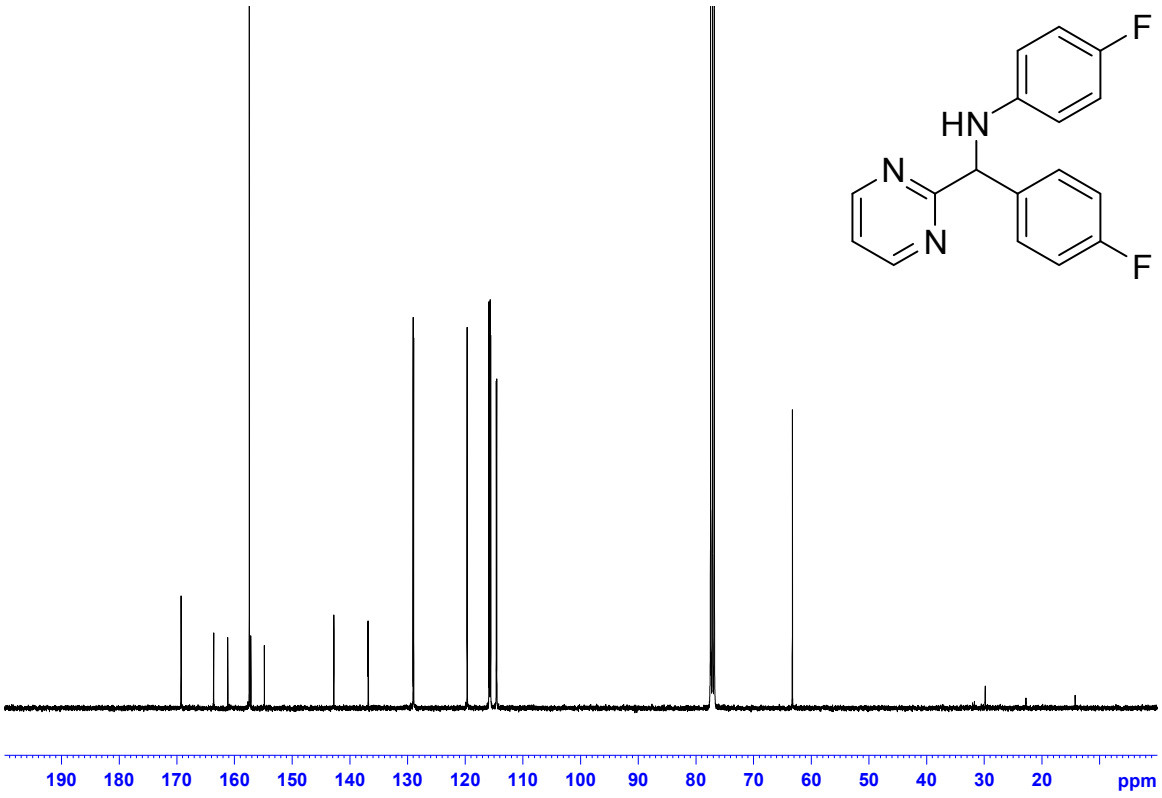
1a ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 296 K)



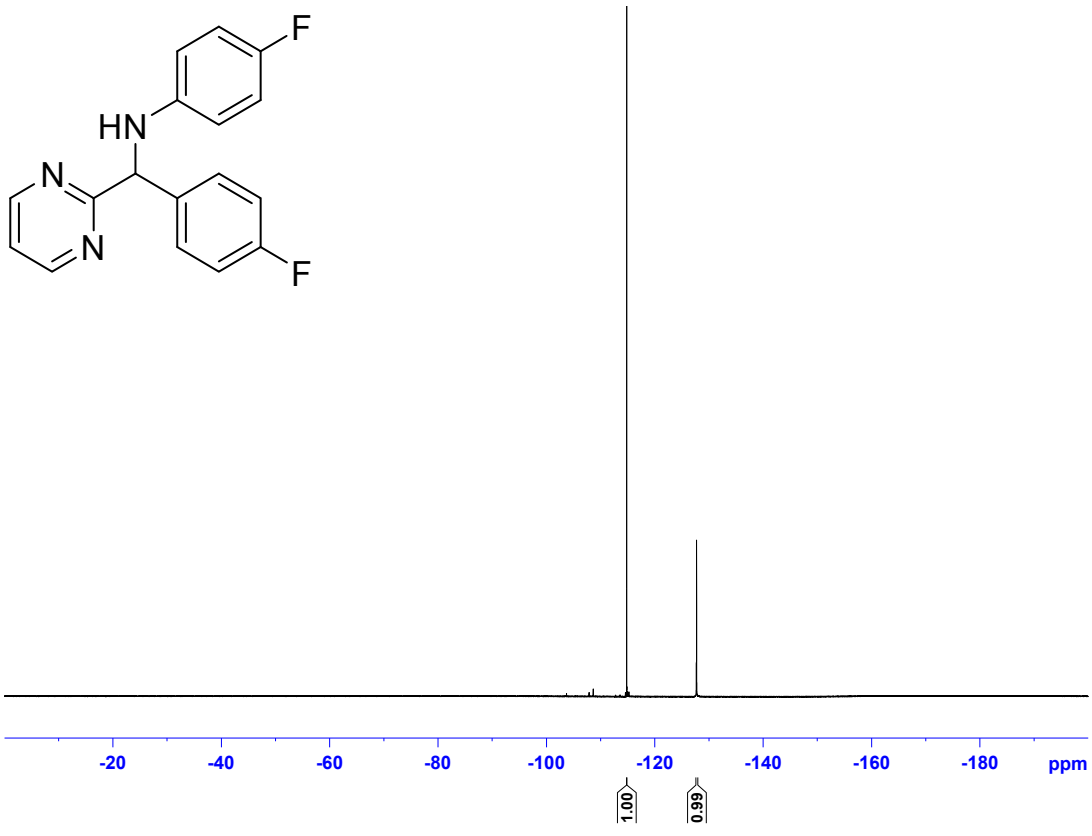
1b (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



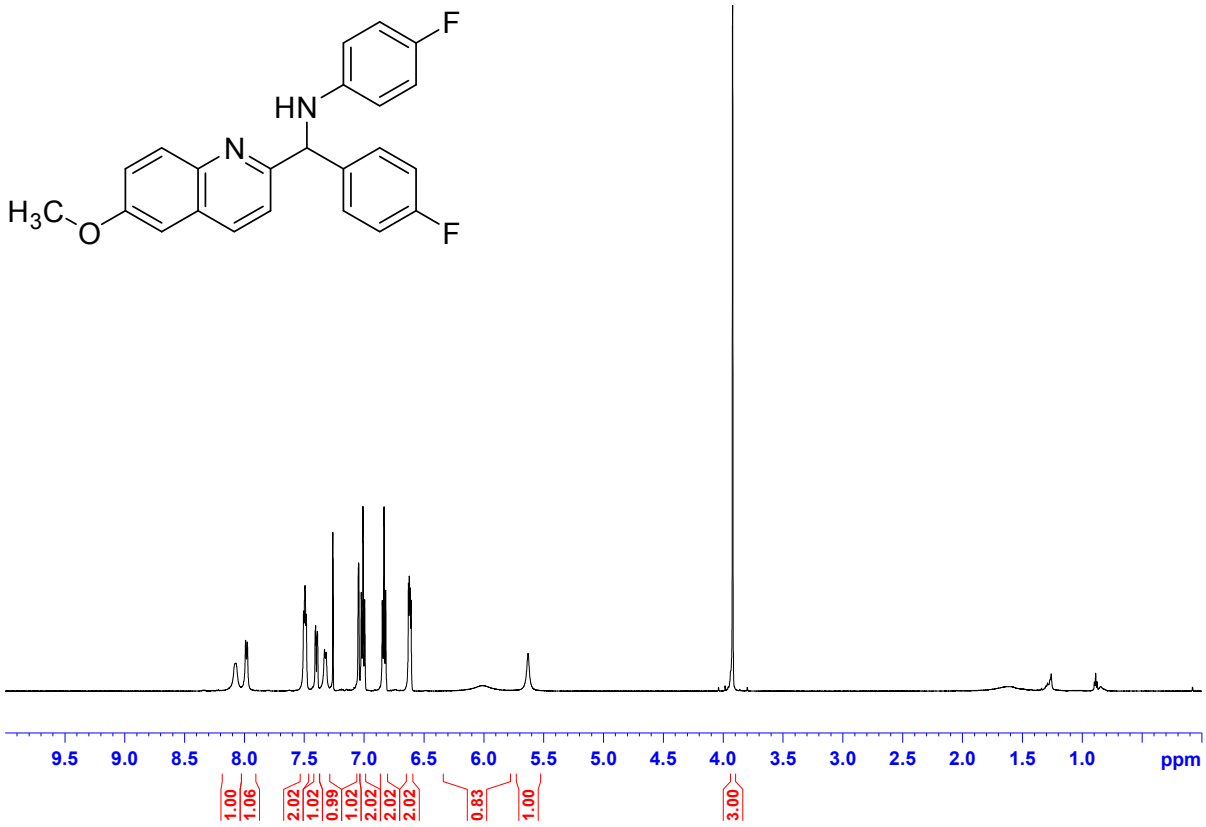
1b ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 299 K)



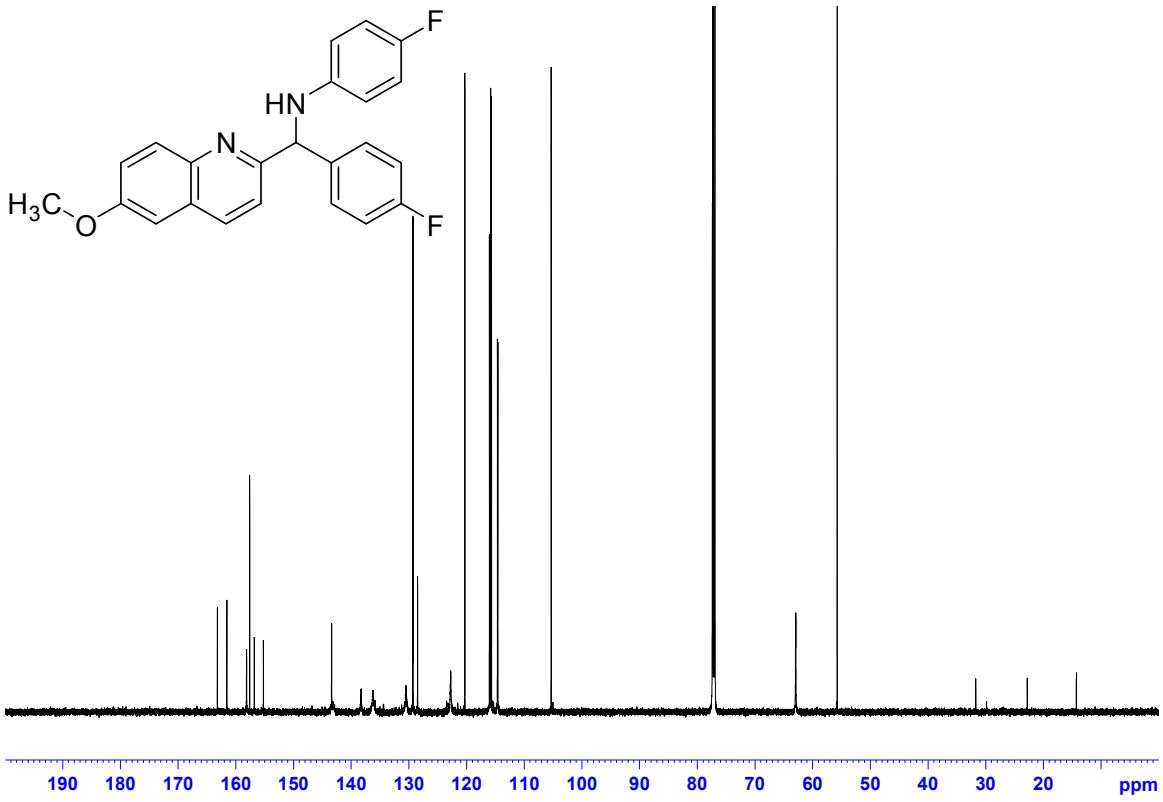
1b ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 297 K)



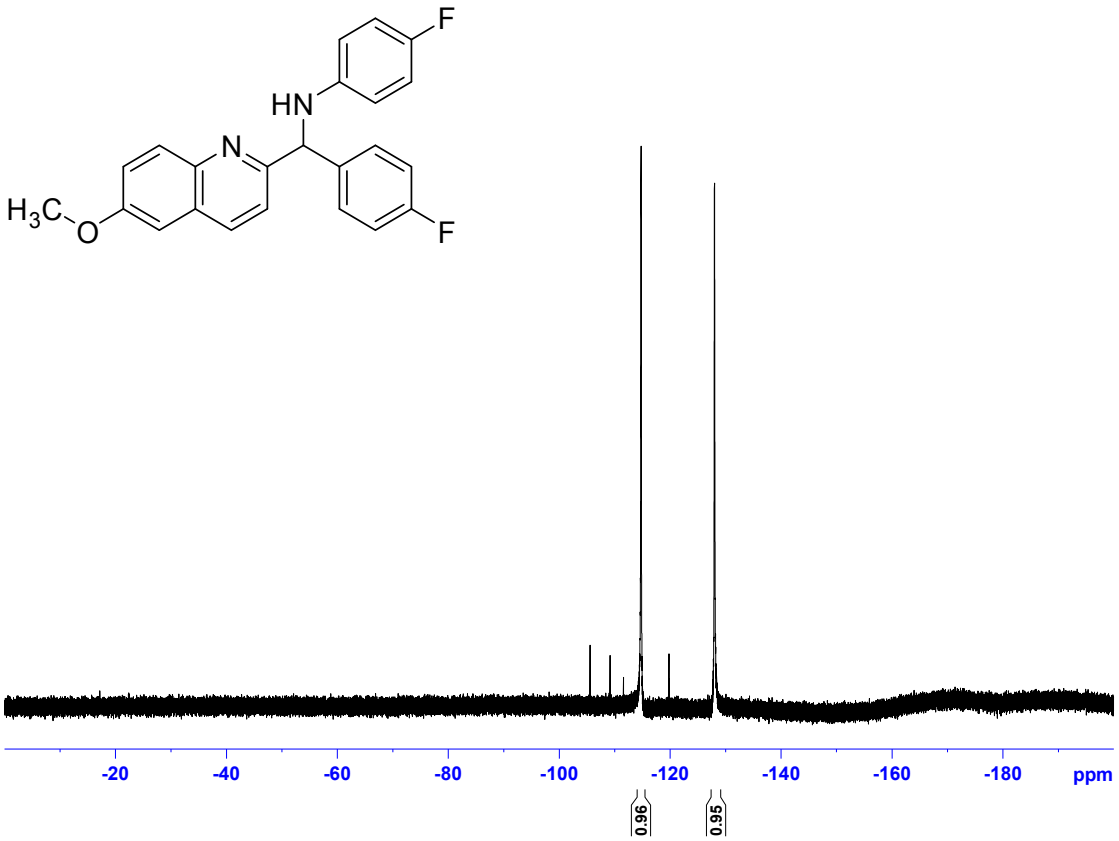
1c (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



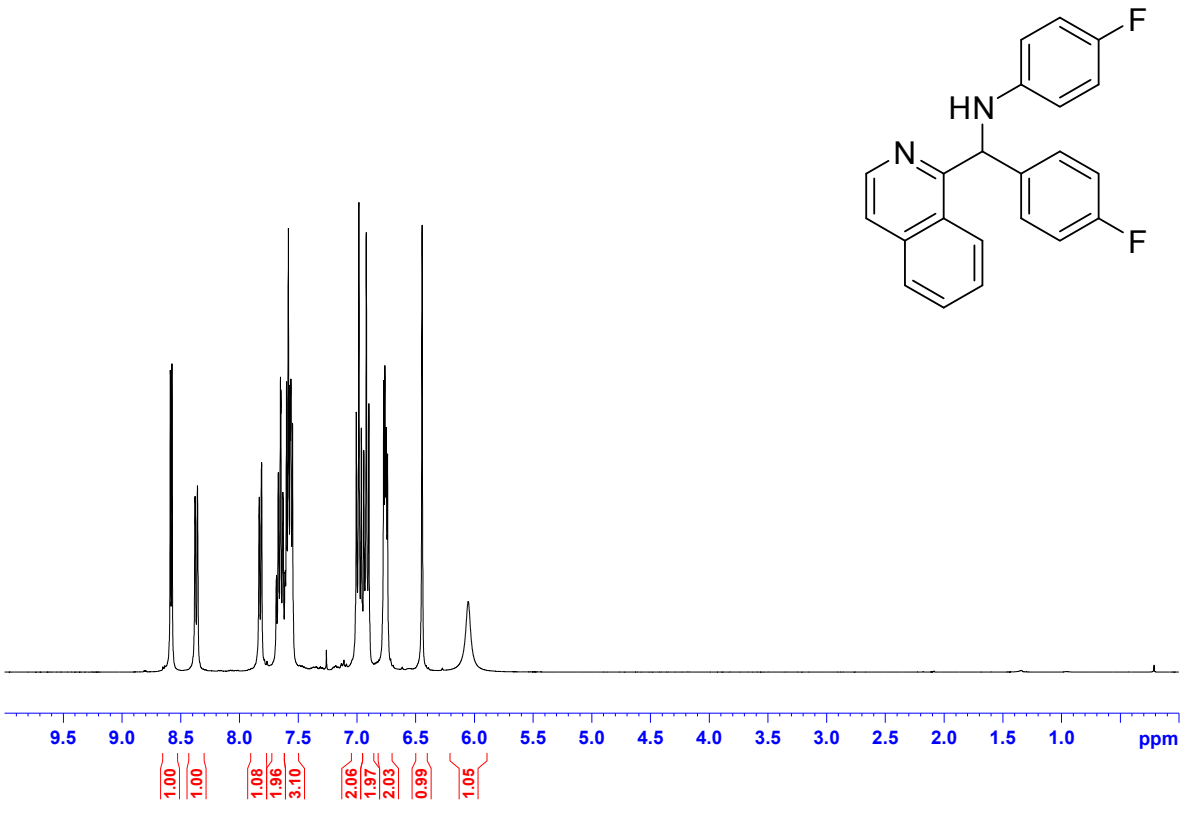
1c (^{13}C{^{1}H} NMR, $CDCl_3$, 150.90 MHz, 295 K)



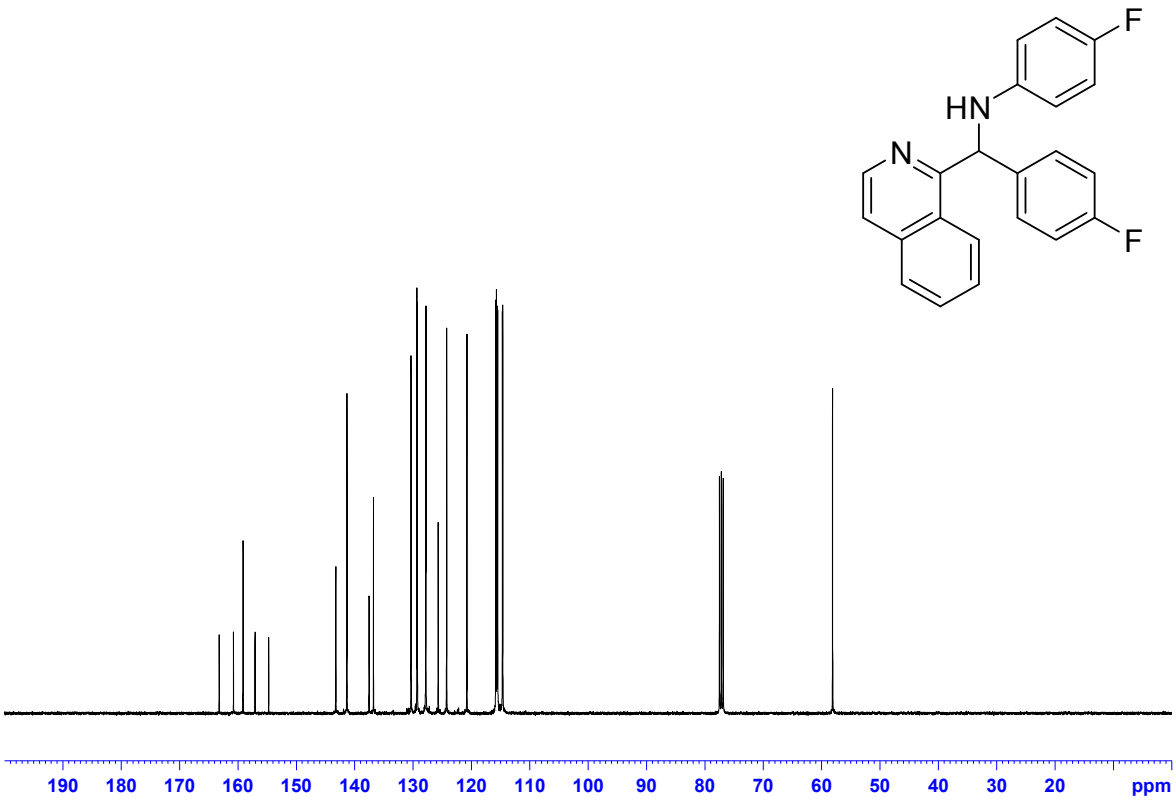
1c ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)



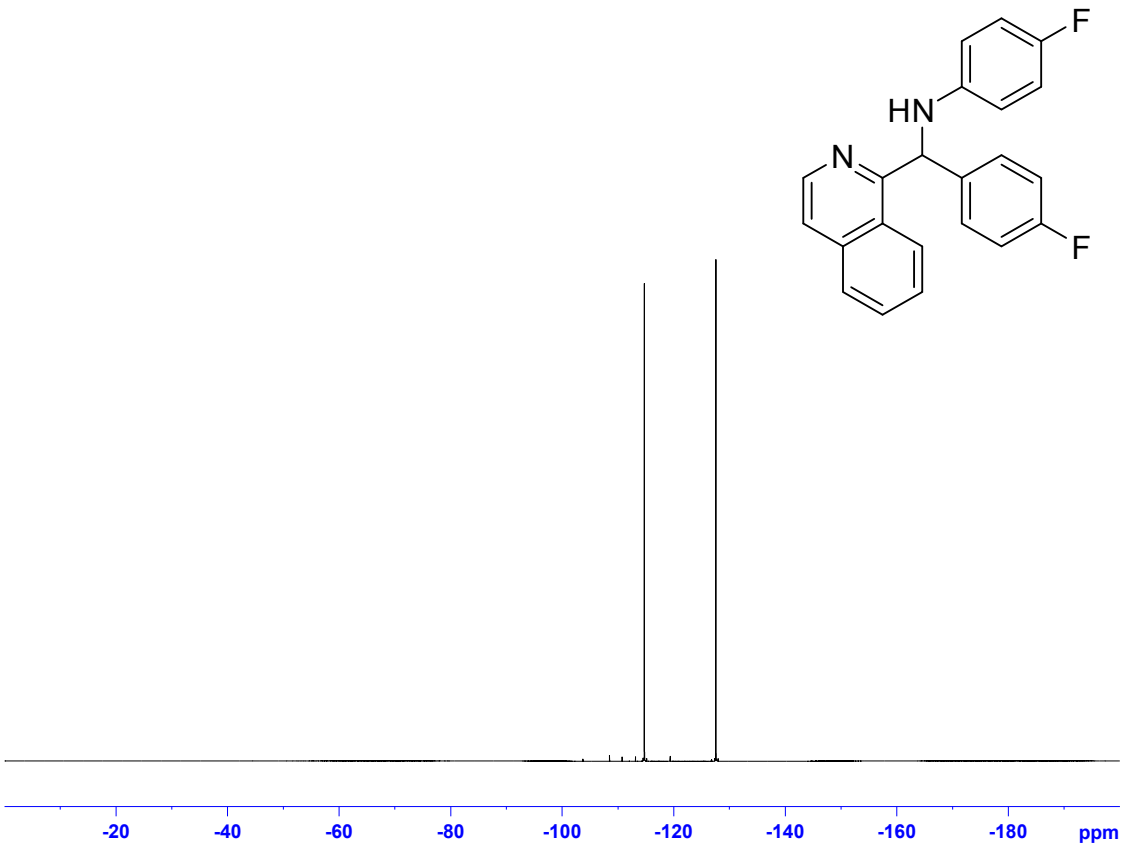
1d (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



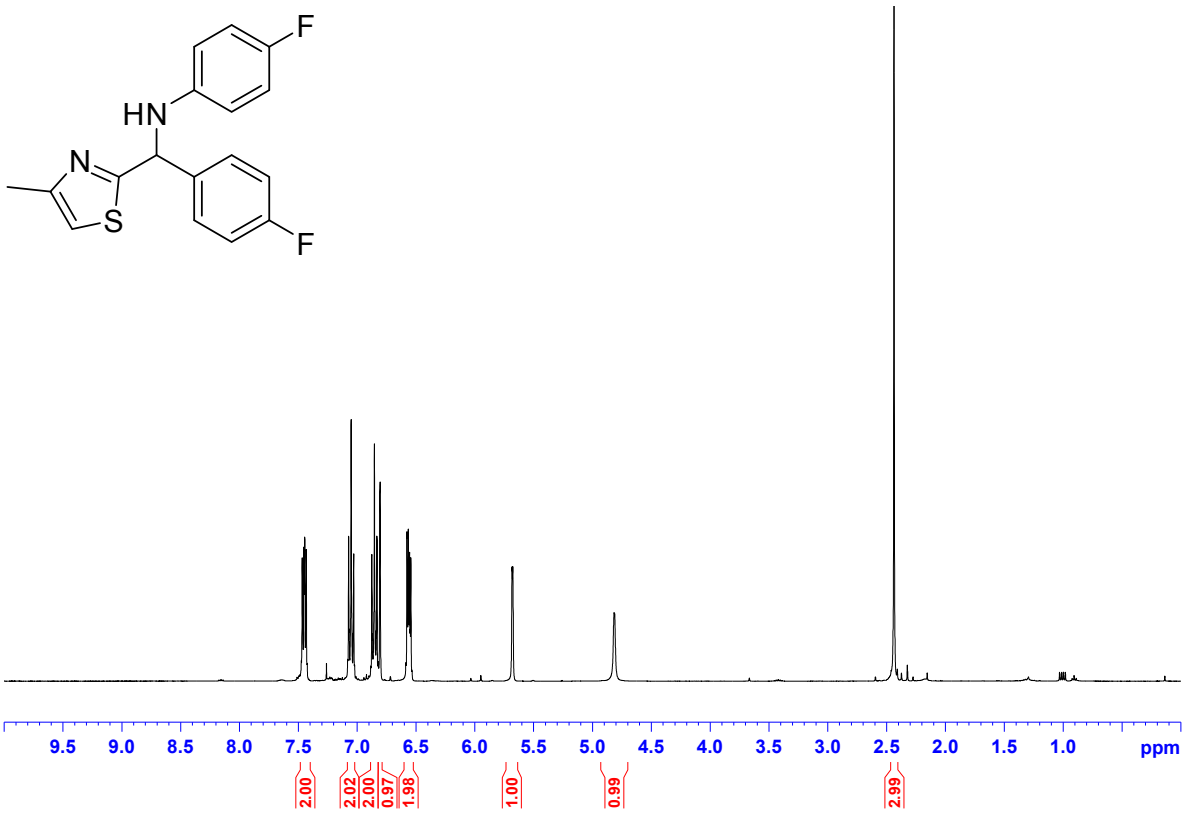
1d ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 297 K)



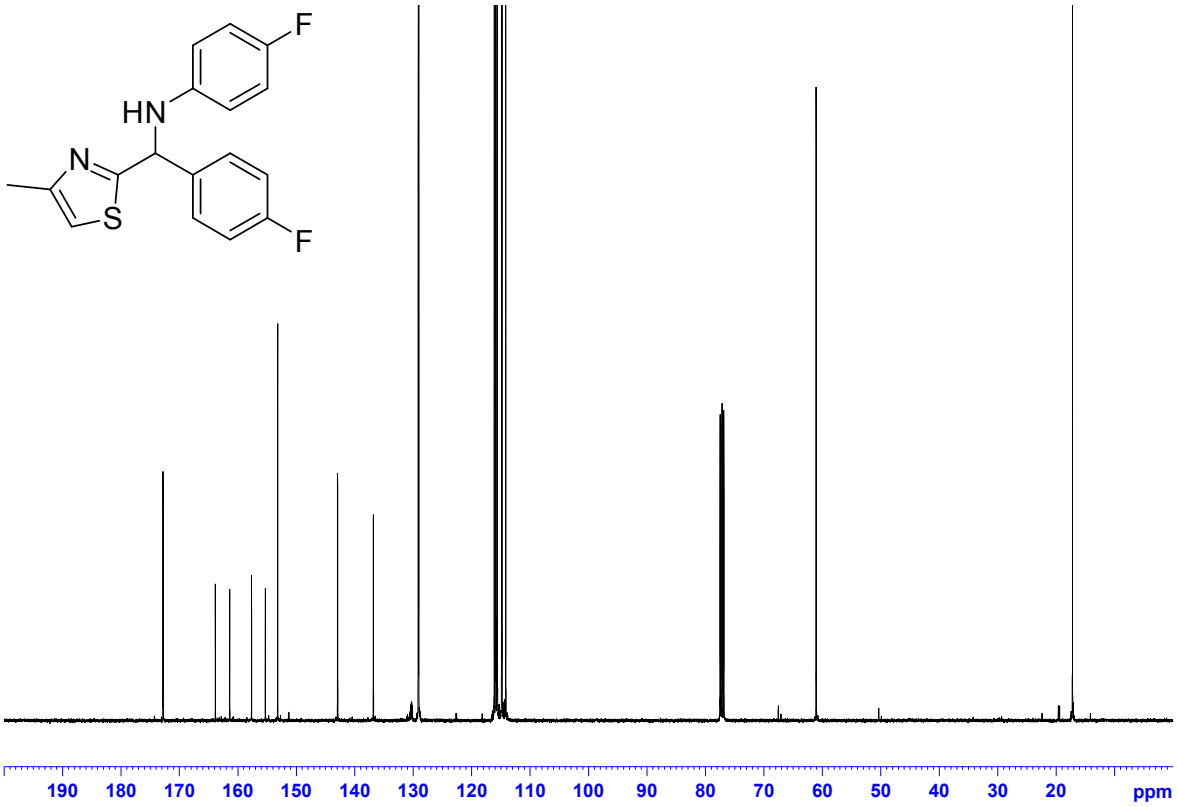
1d ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 296 K)



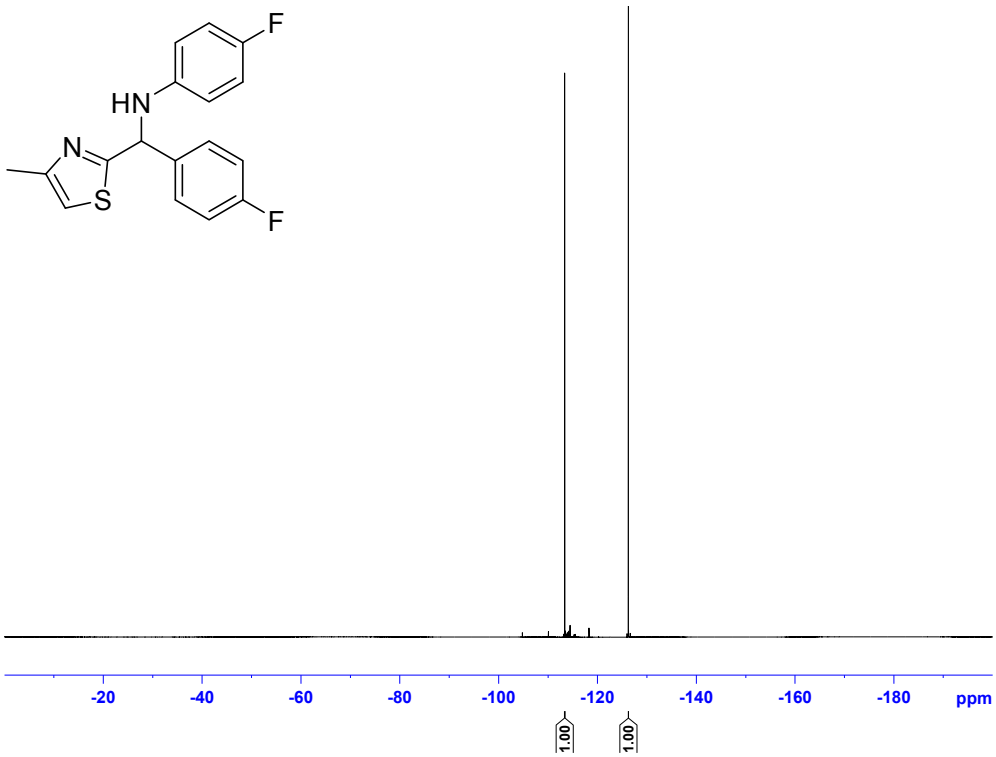
1e (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



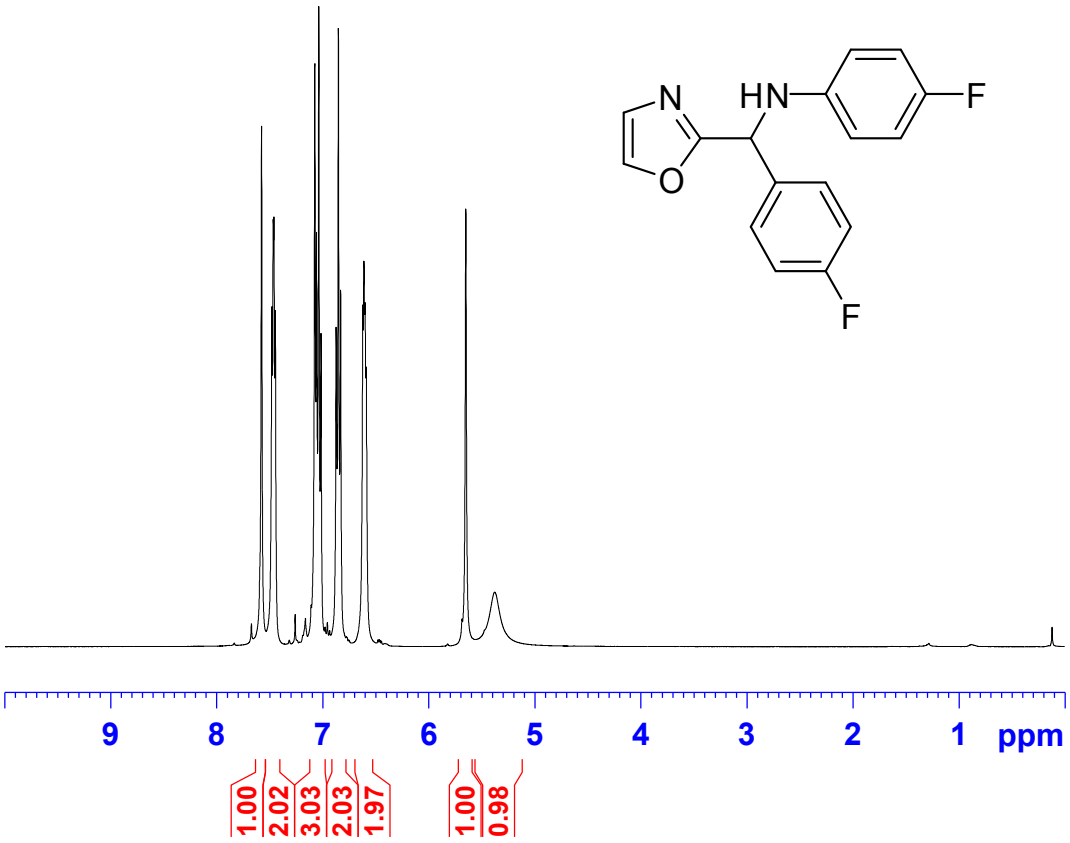
1e ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 298 K)



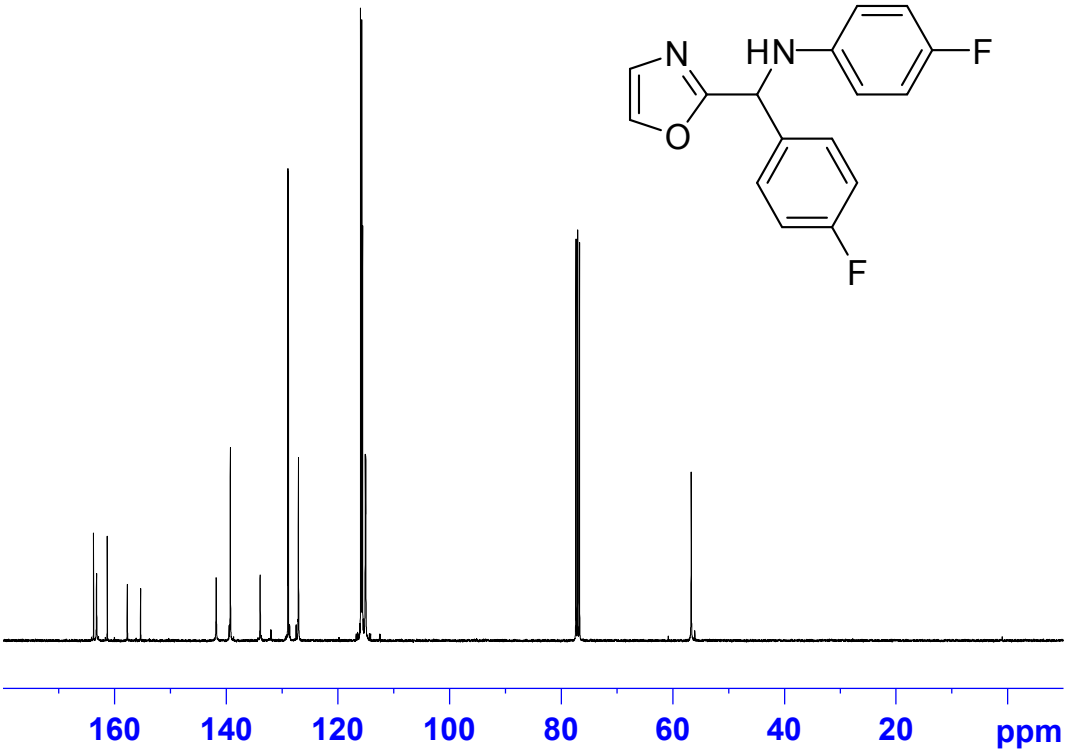
1e ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 297 K)



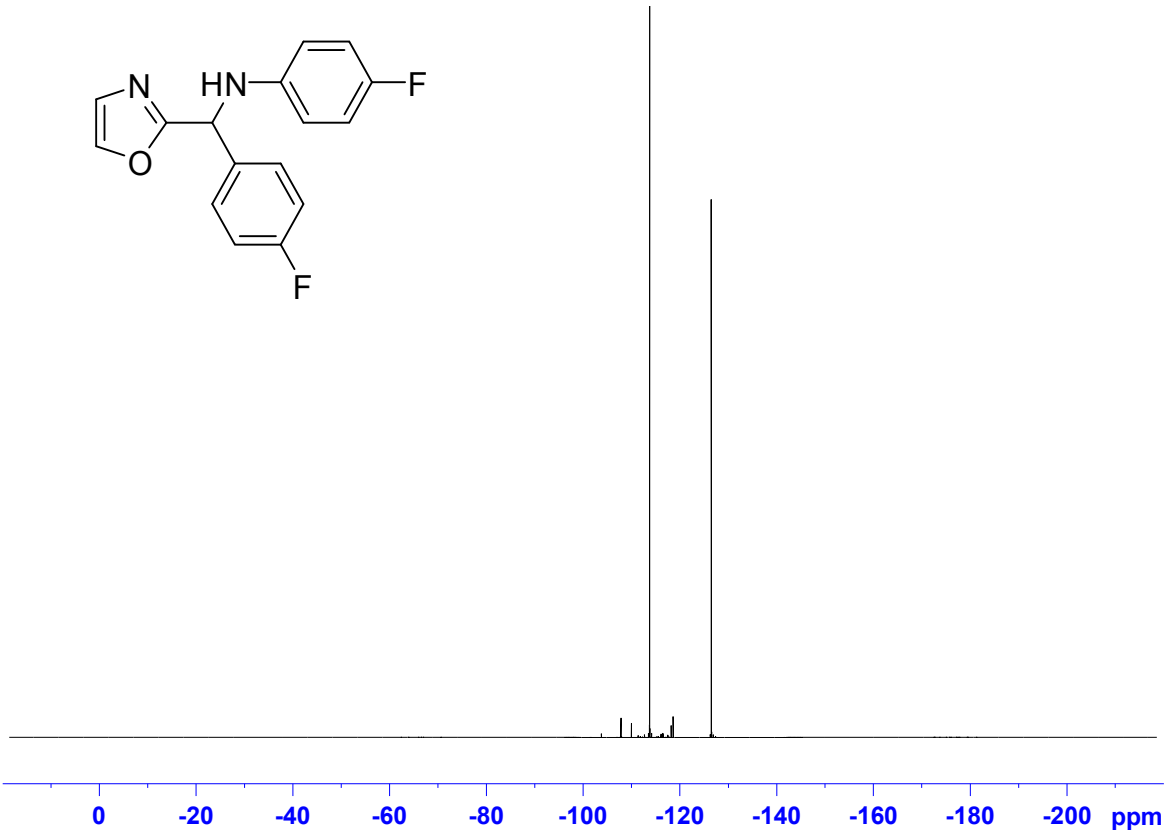
1f (^{1}H NMR, $CDCl_3$, 399.89 MHz, 296 K)



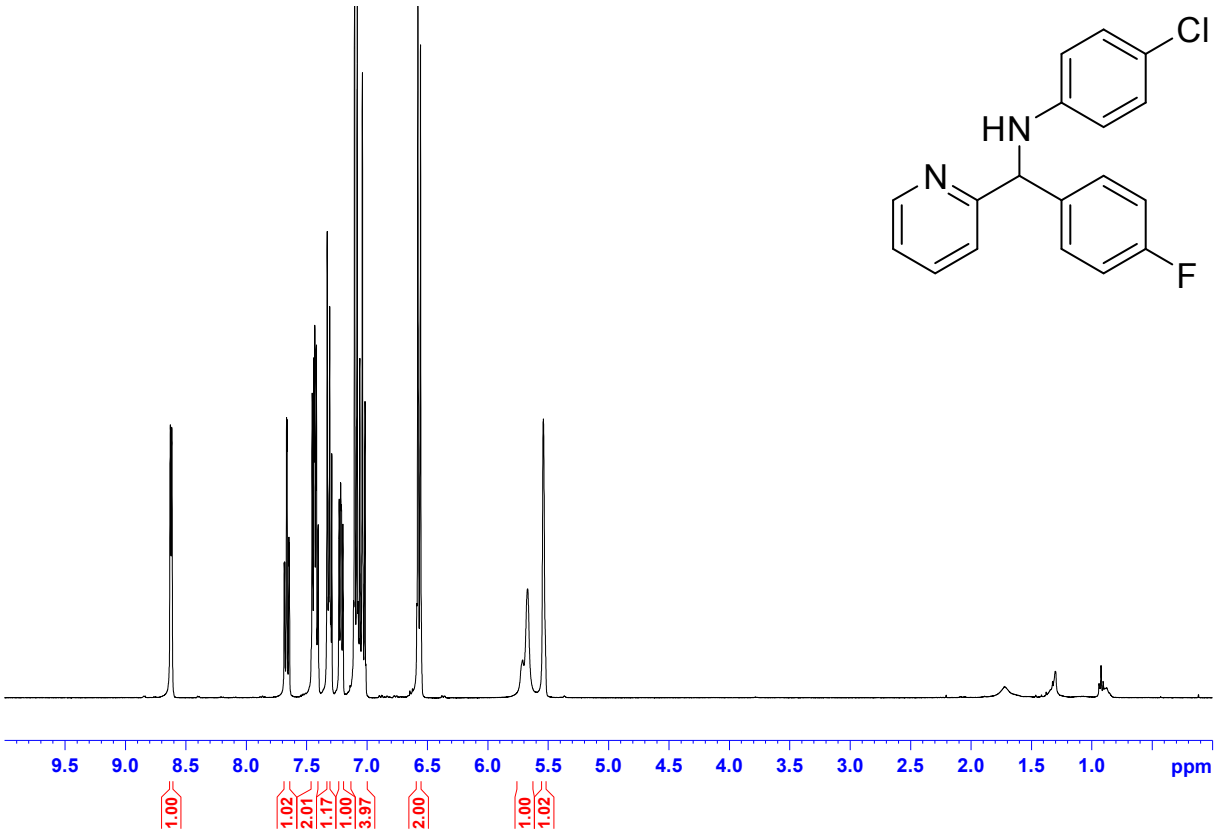
1f ($^{13}C\{^{1}H\}$ NMR, C_6D_6D, 100.55 MHz, 297 K)



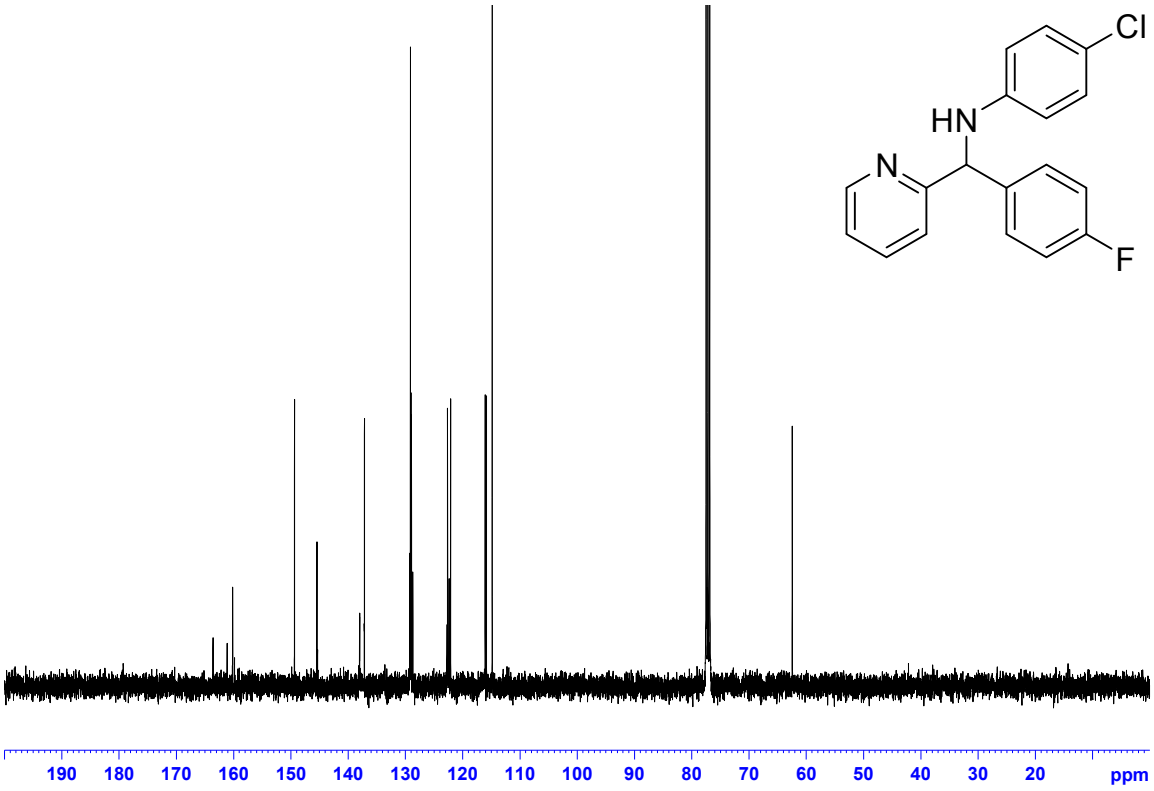
1f ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 298 K)



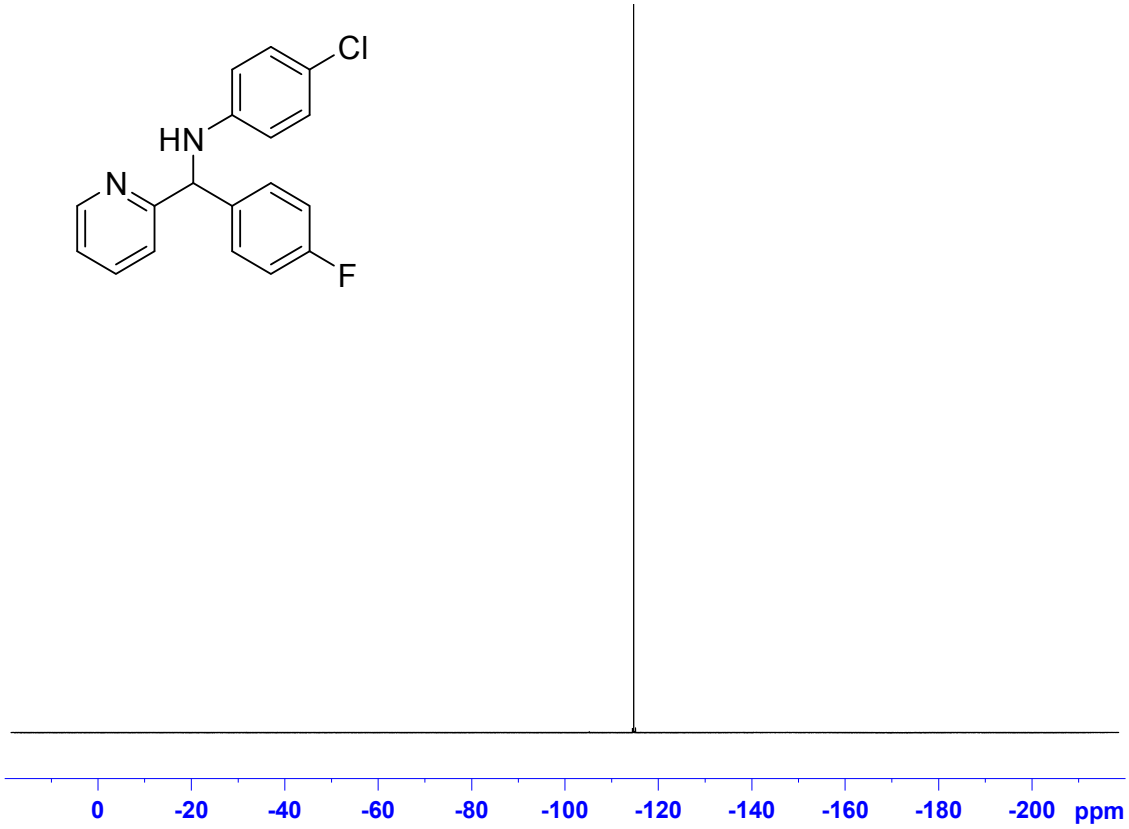
2a (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



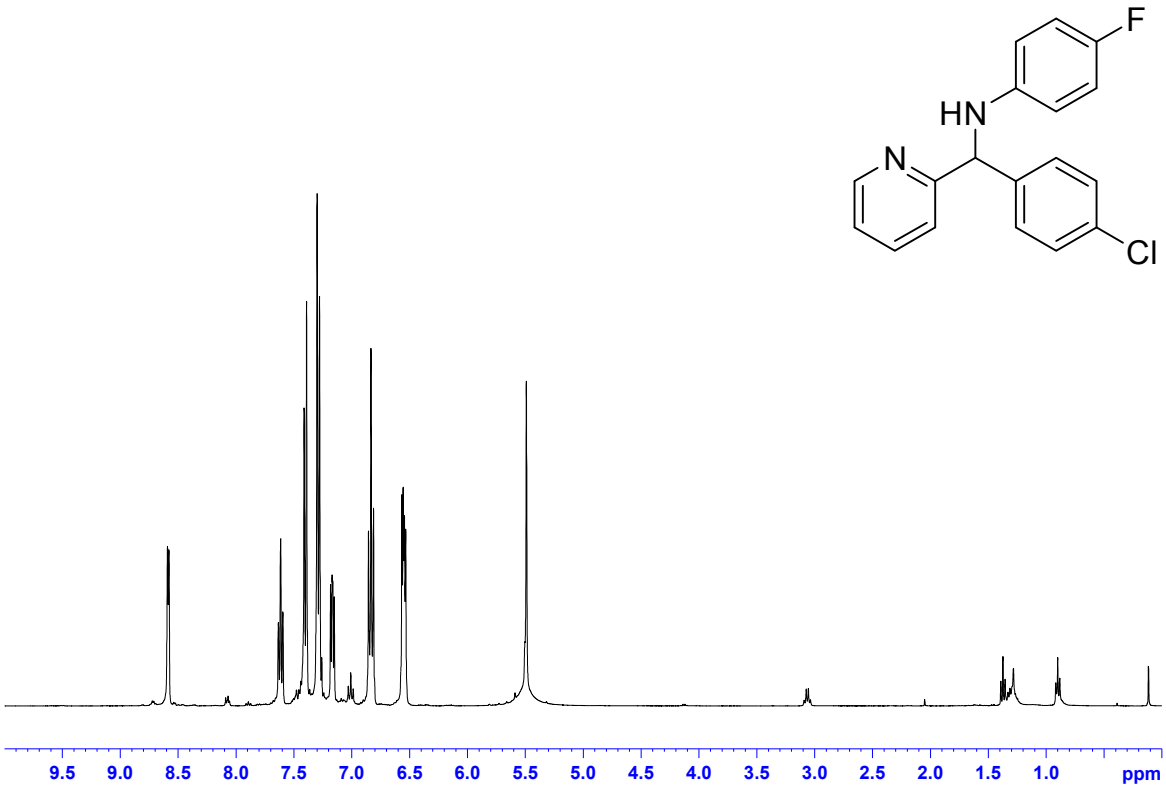
2a (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 295 K)



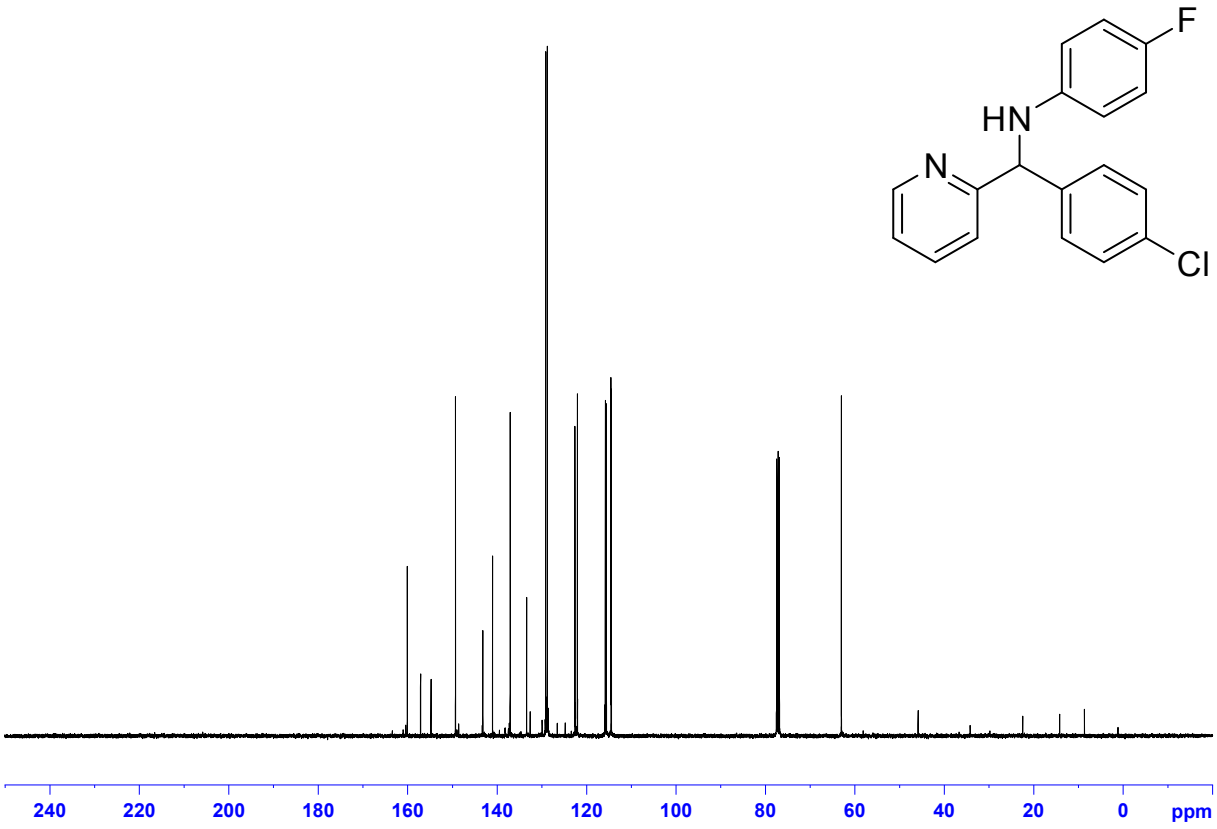
2a ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)



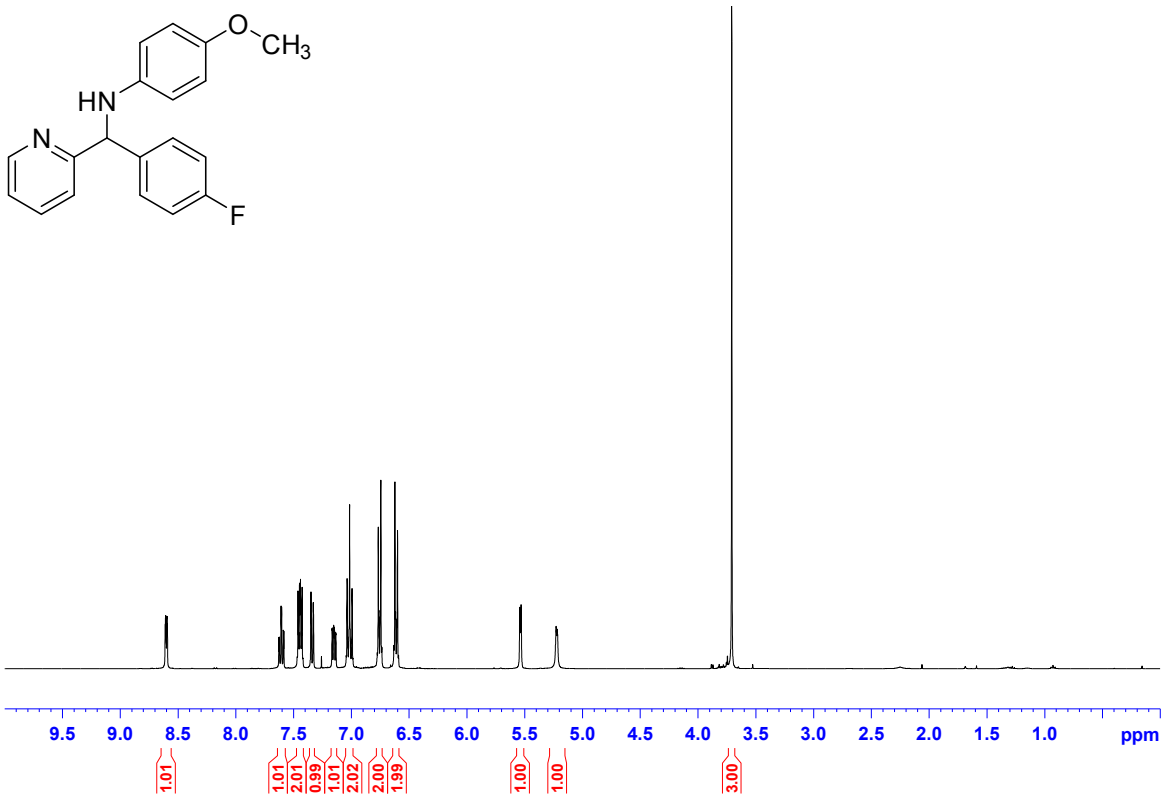
2b (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



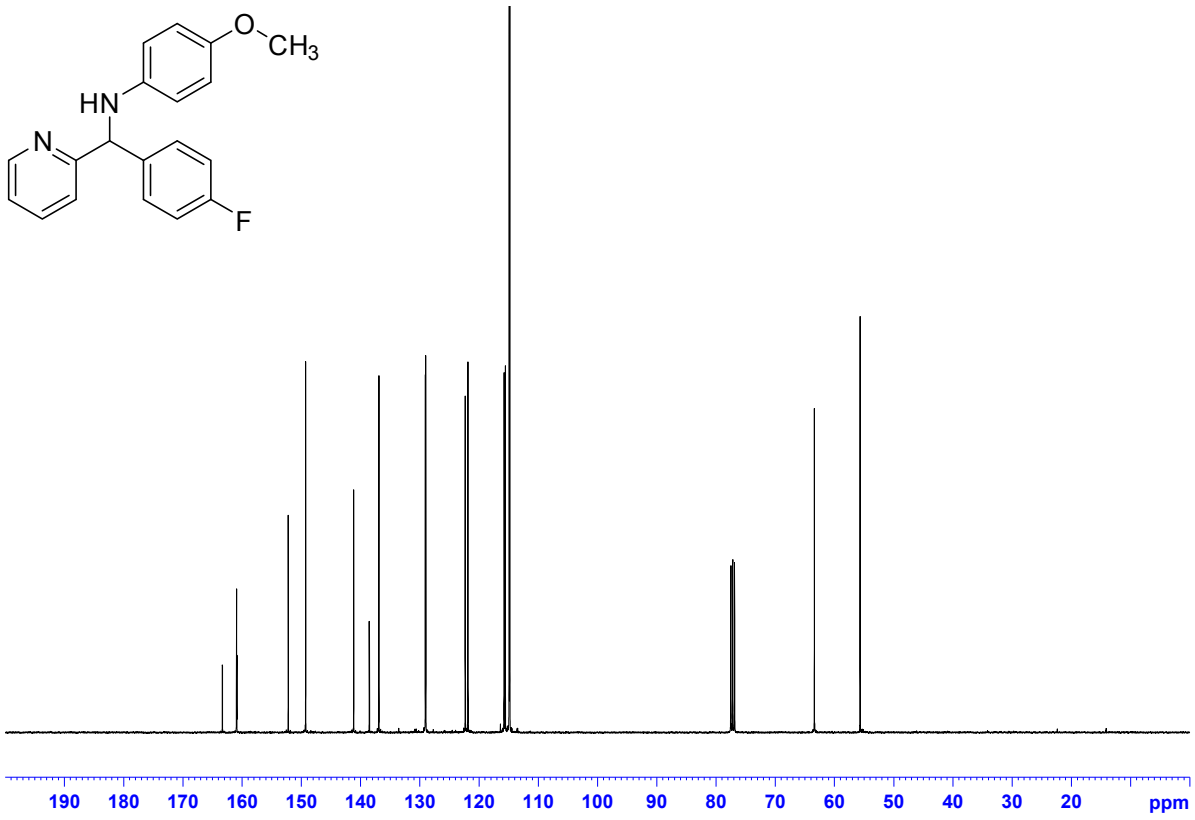
2b ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 295 K)



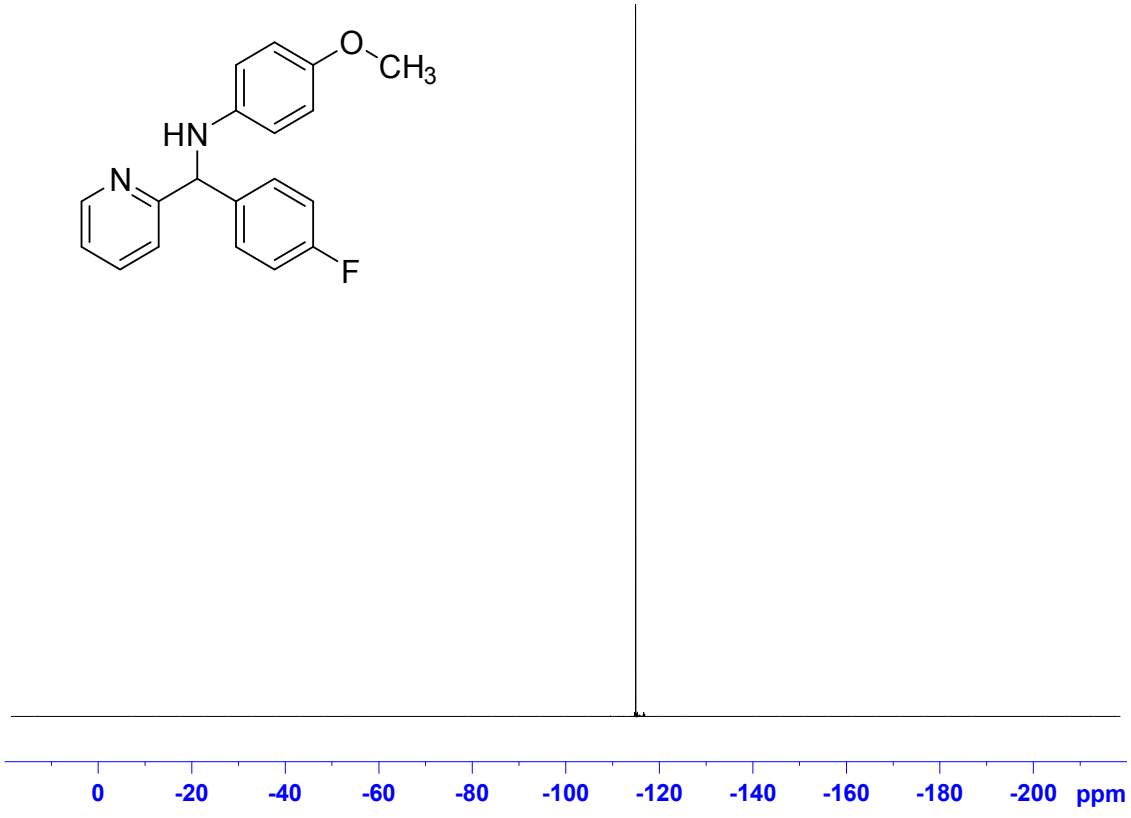
2b (^{1}H NMR, $CDCl_3$, 399.89 MHz, 296 K)



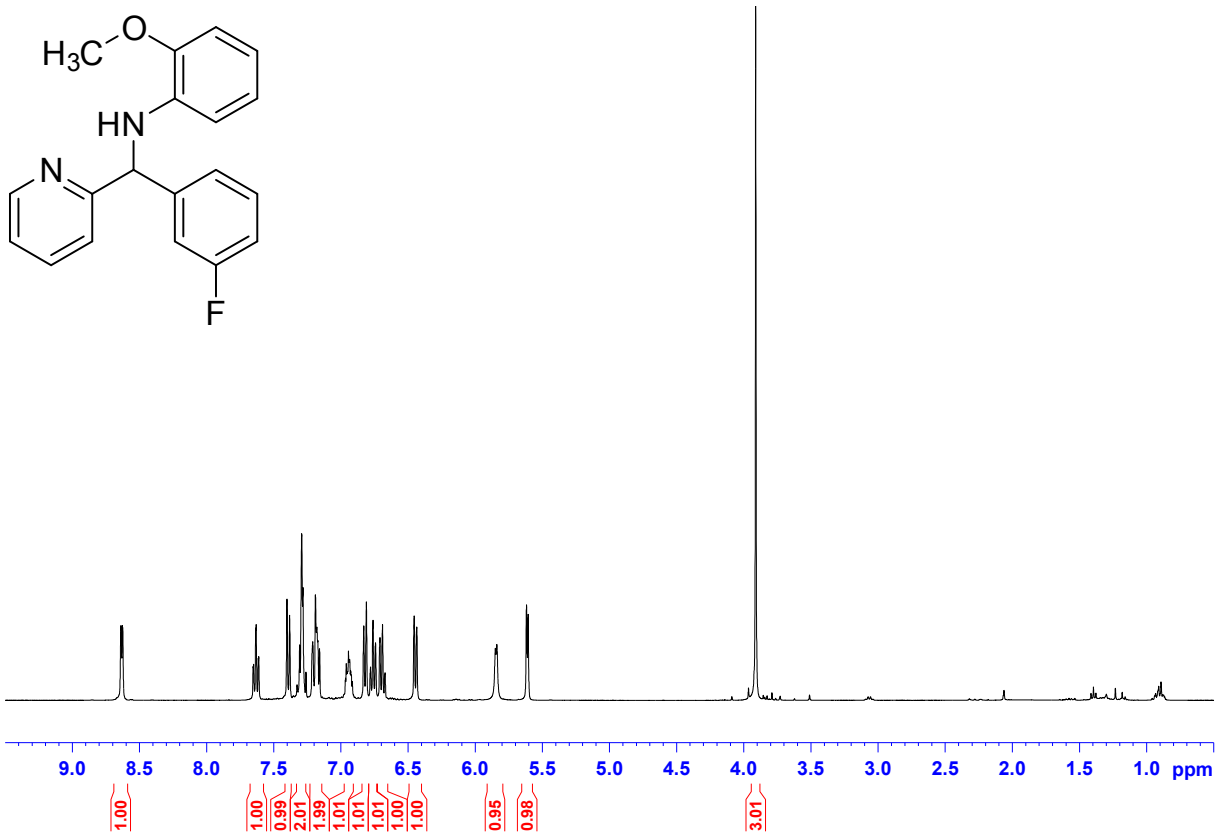
2c ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 298 K)



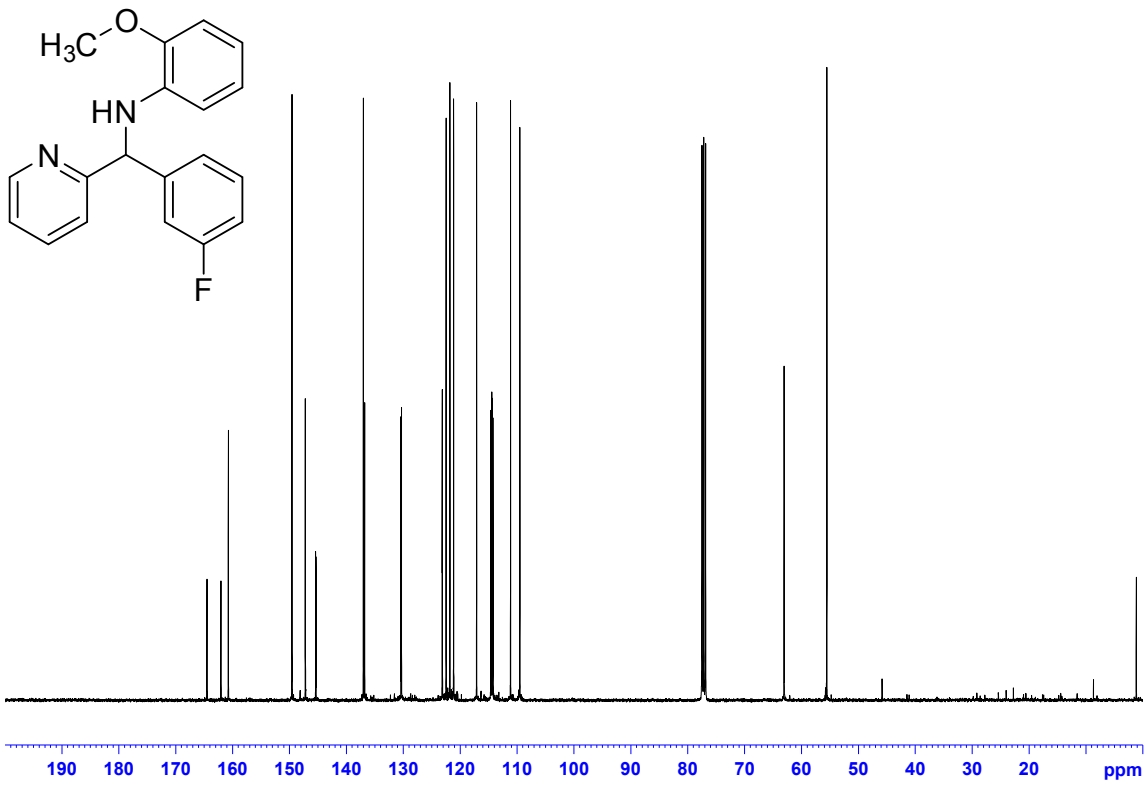
2c ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 297 K)



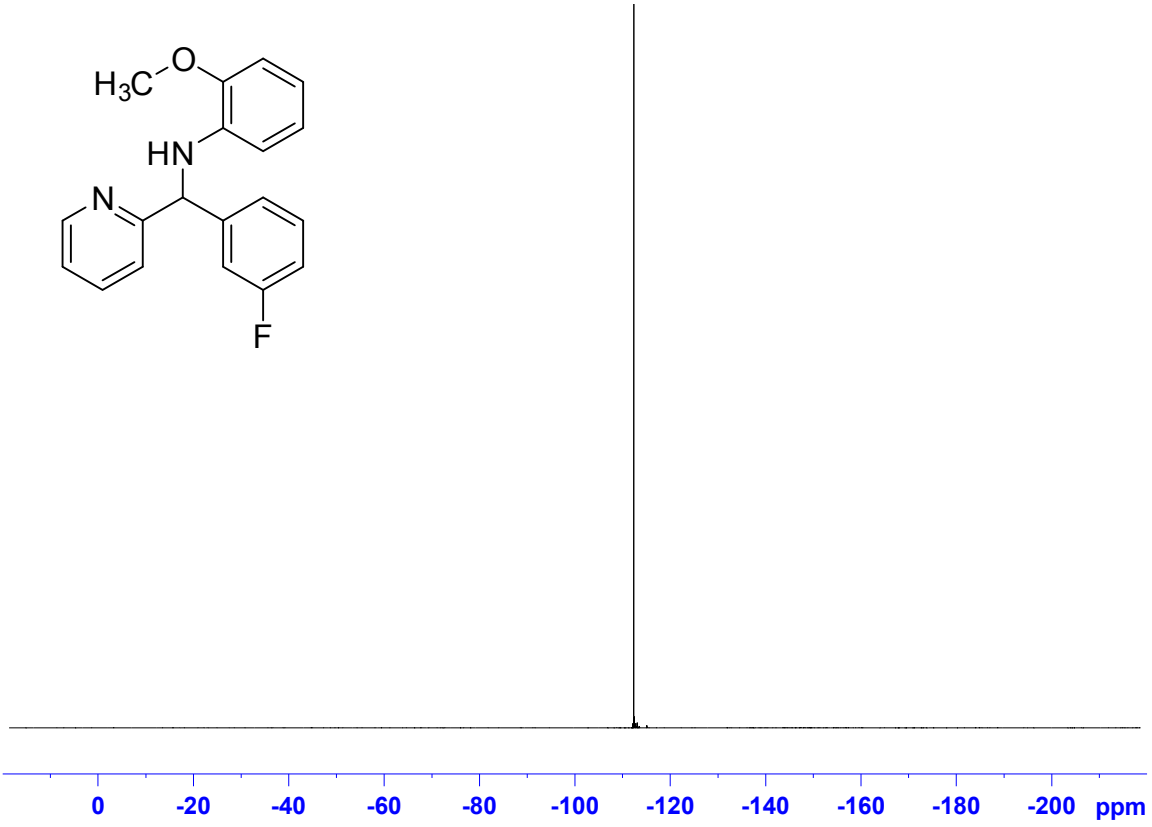
2d (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



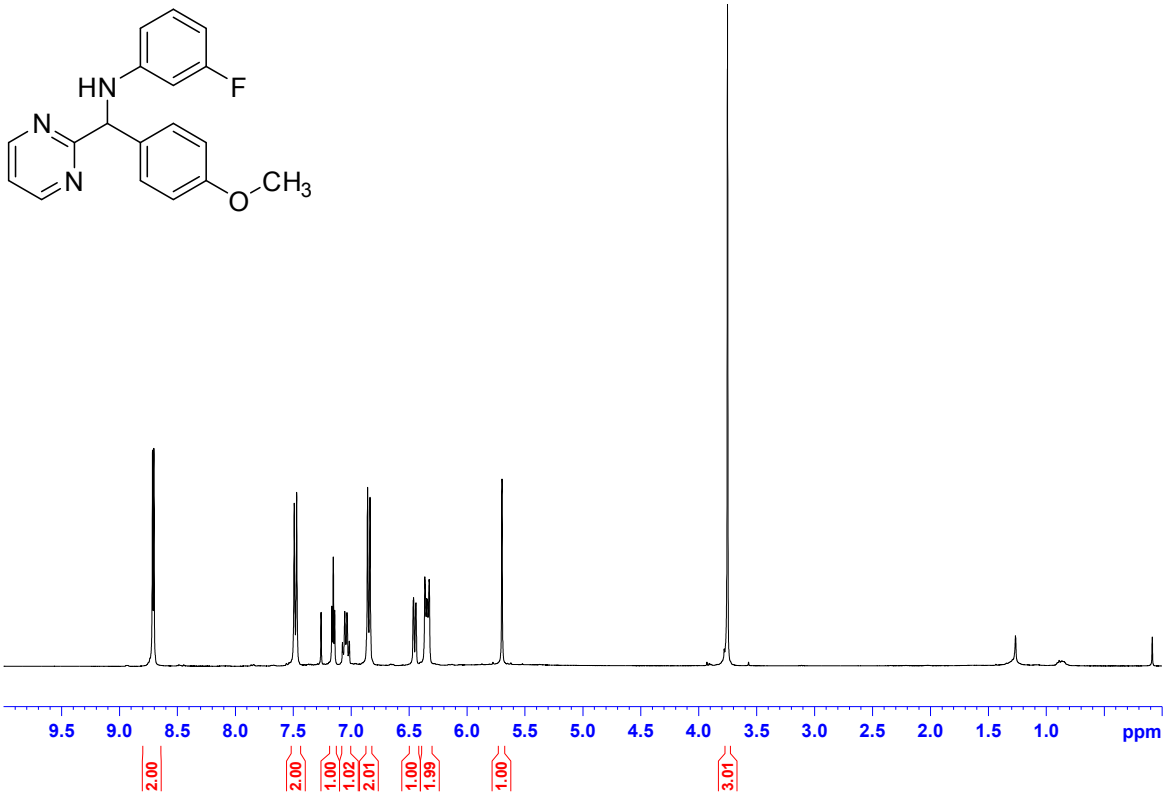
2d (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 299 K)



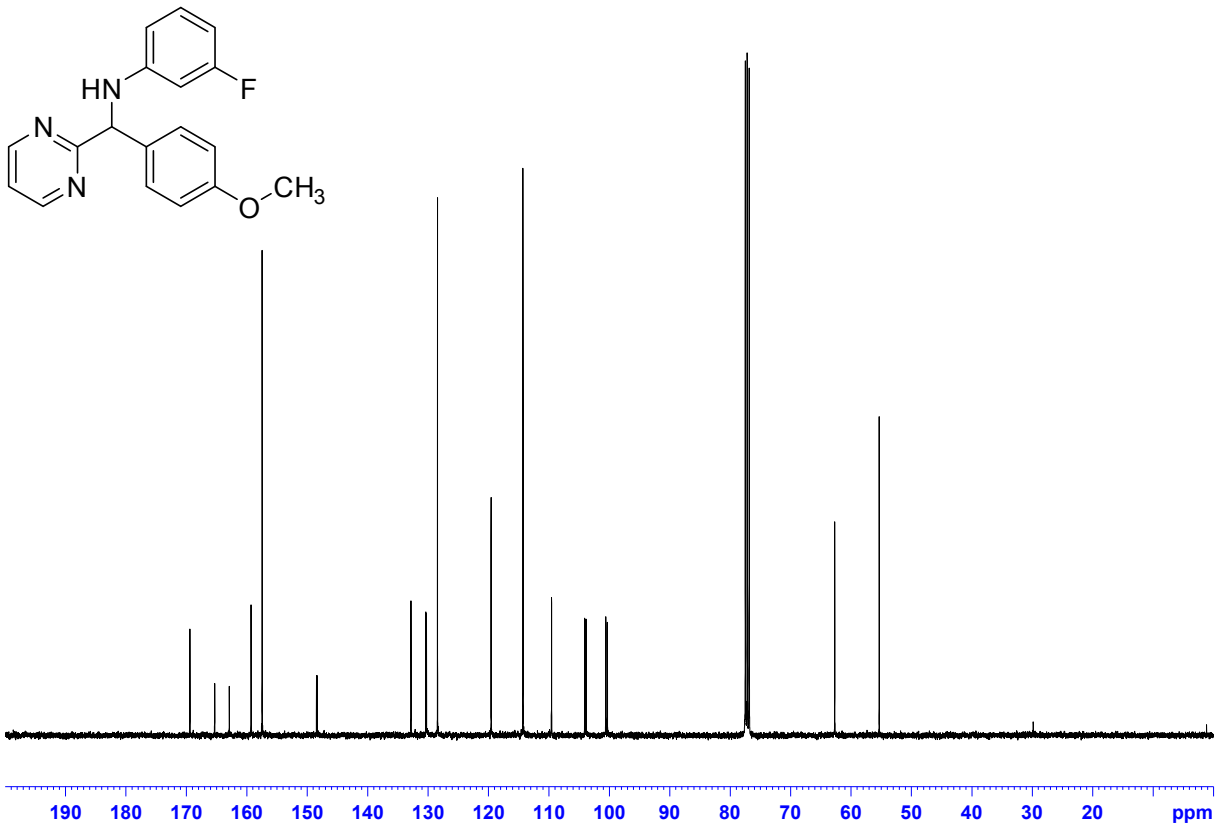
2d ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 298 K)



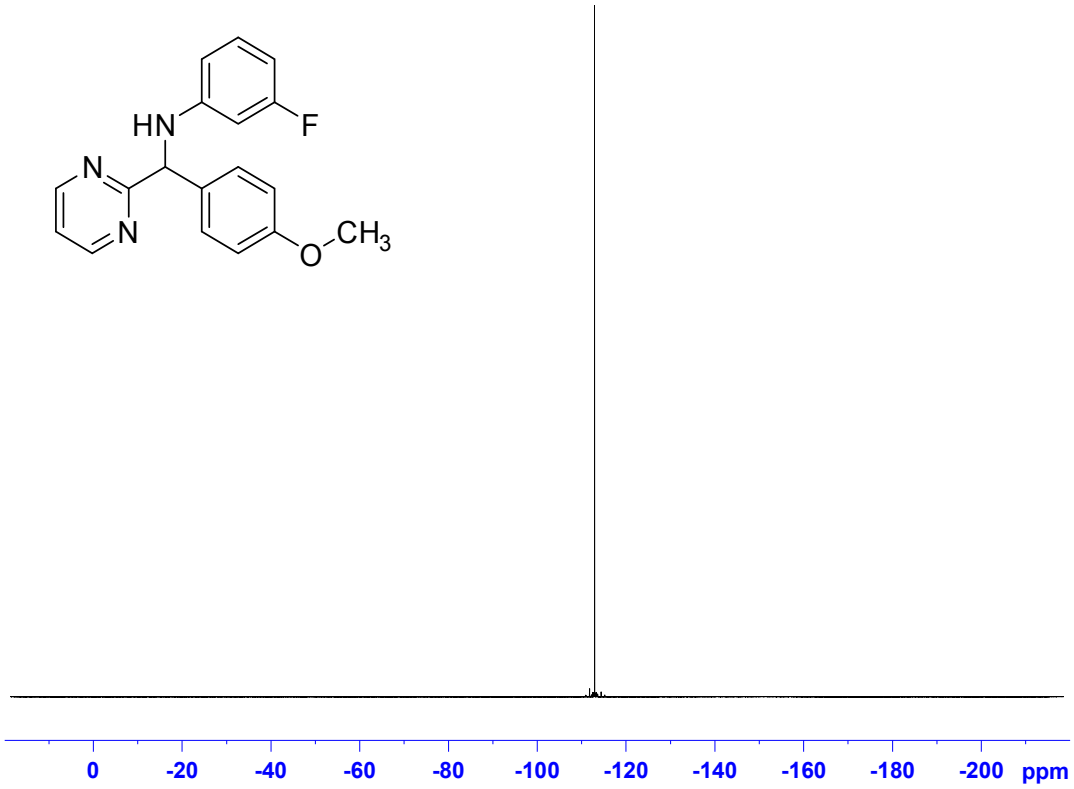
2e (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



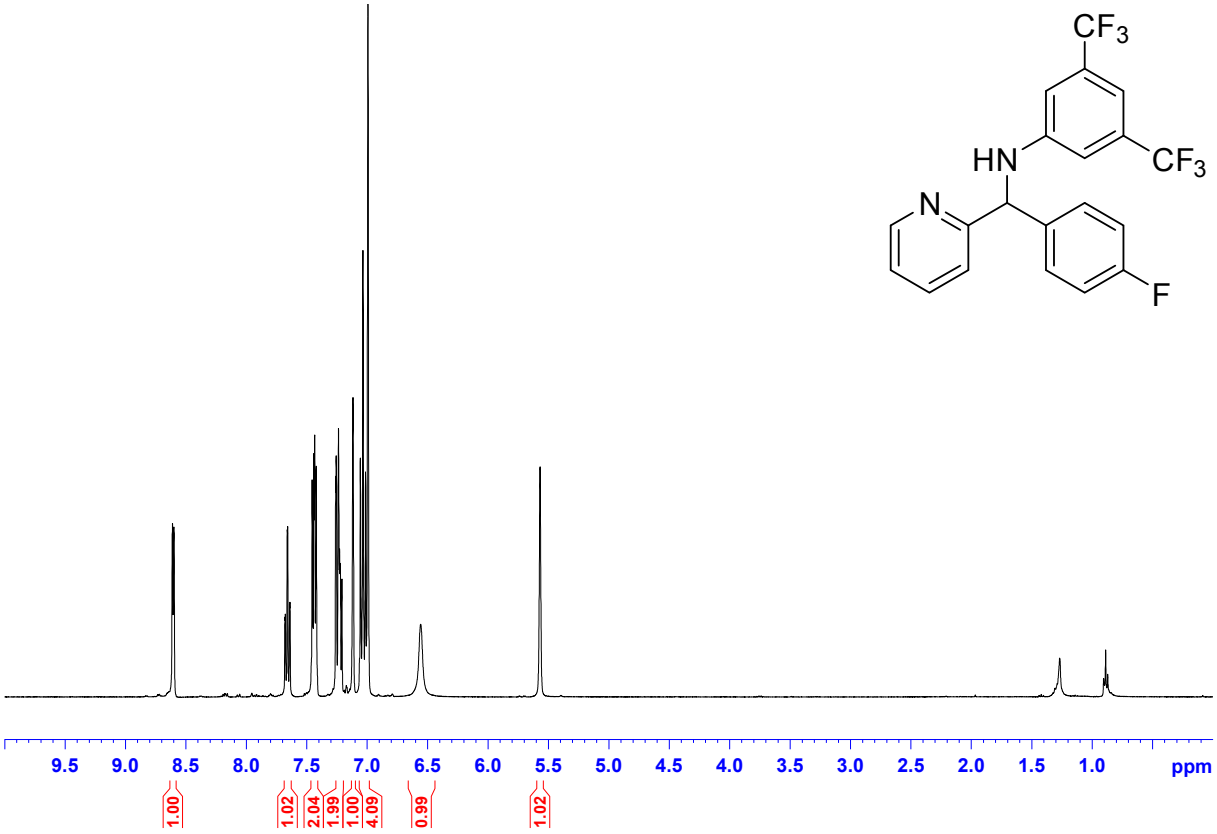
2e ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 295 K)



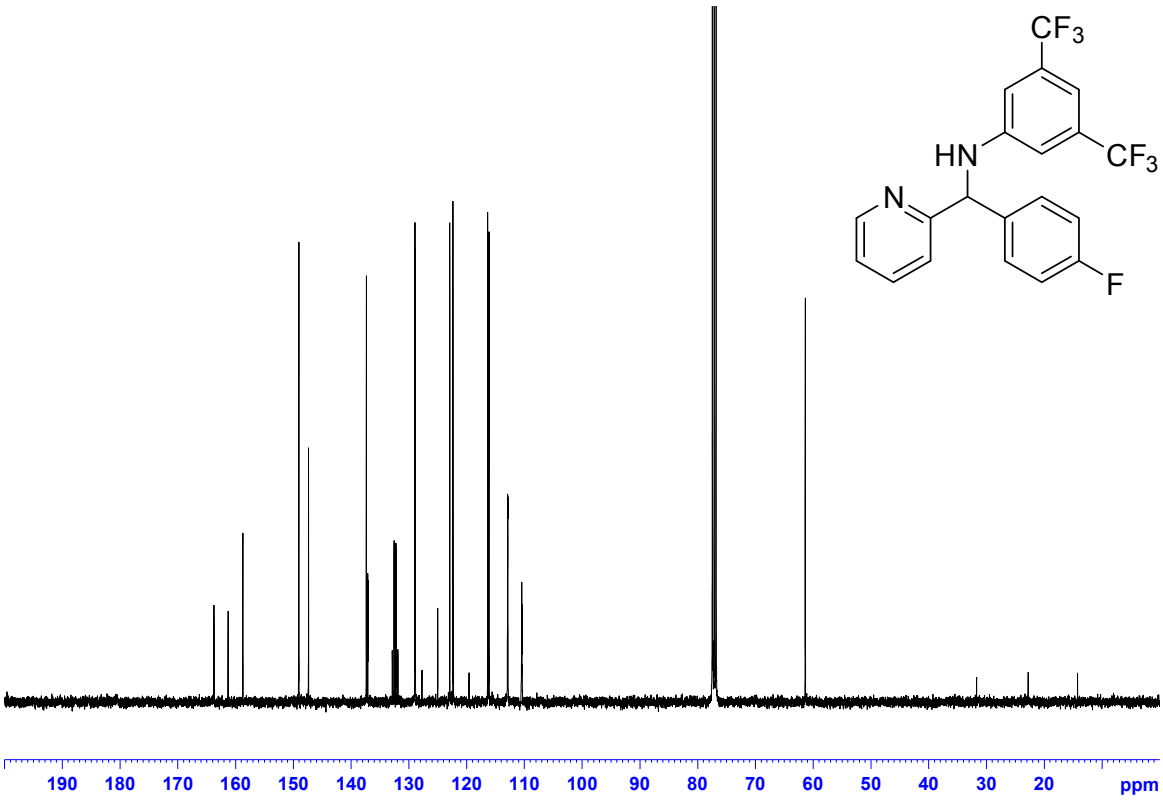
2e ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)



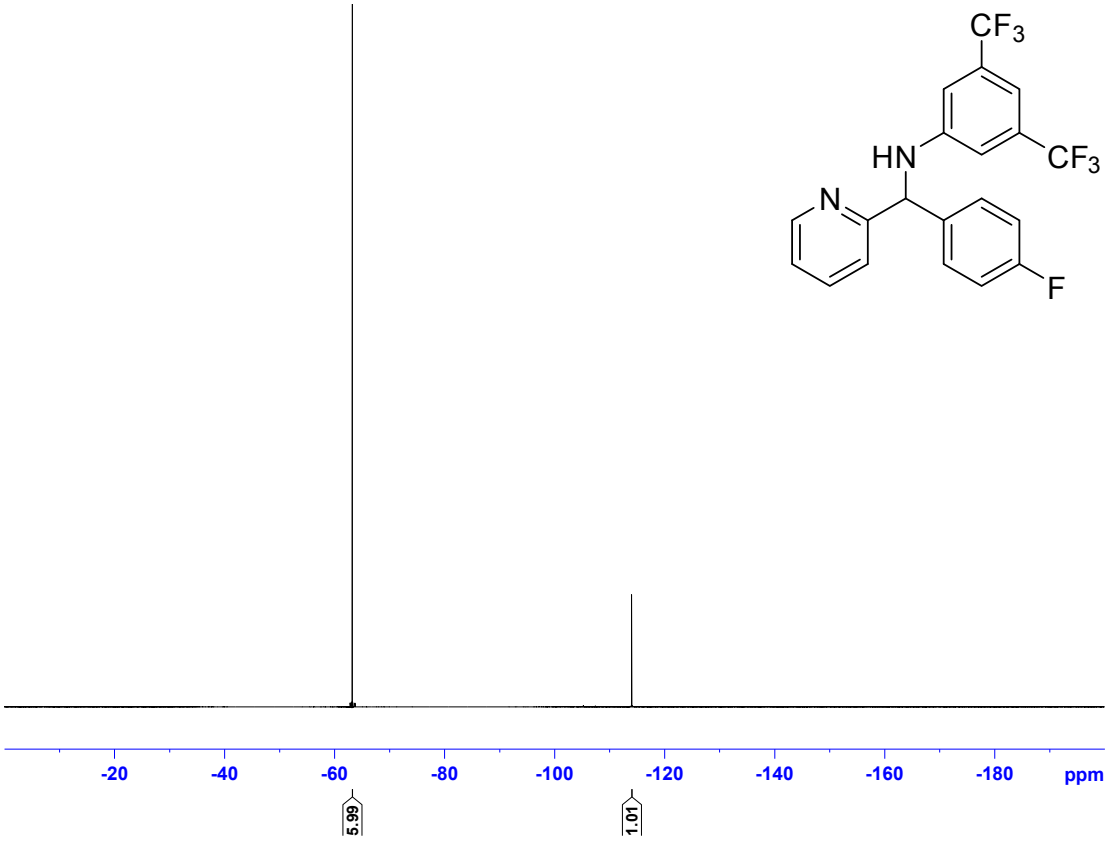
2f (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



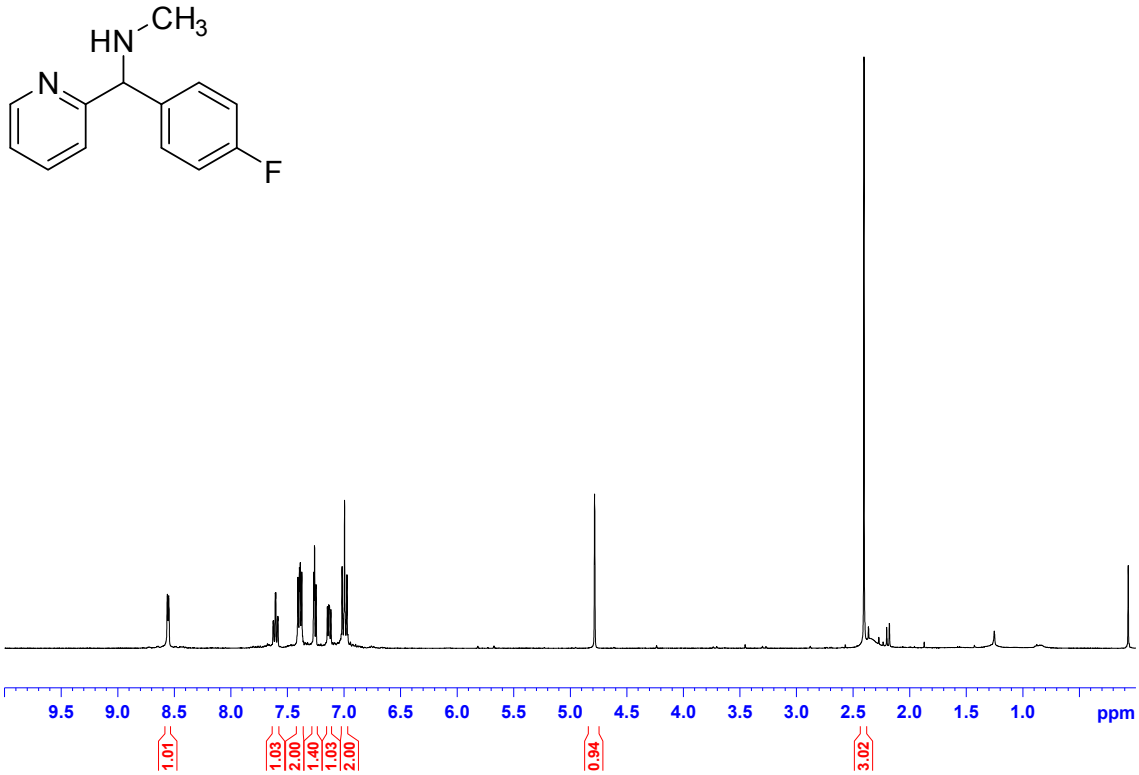
2f (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 295 K)



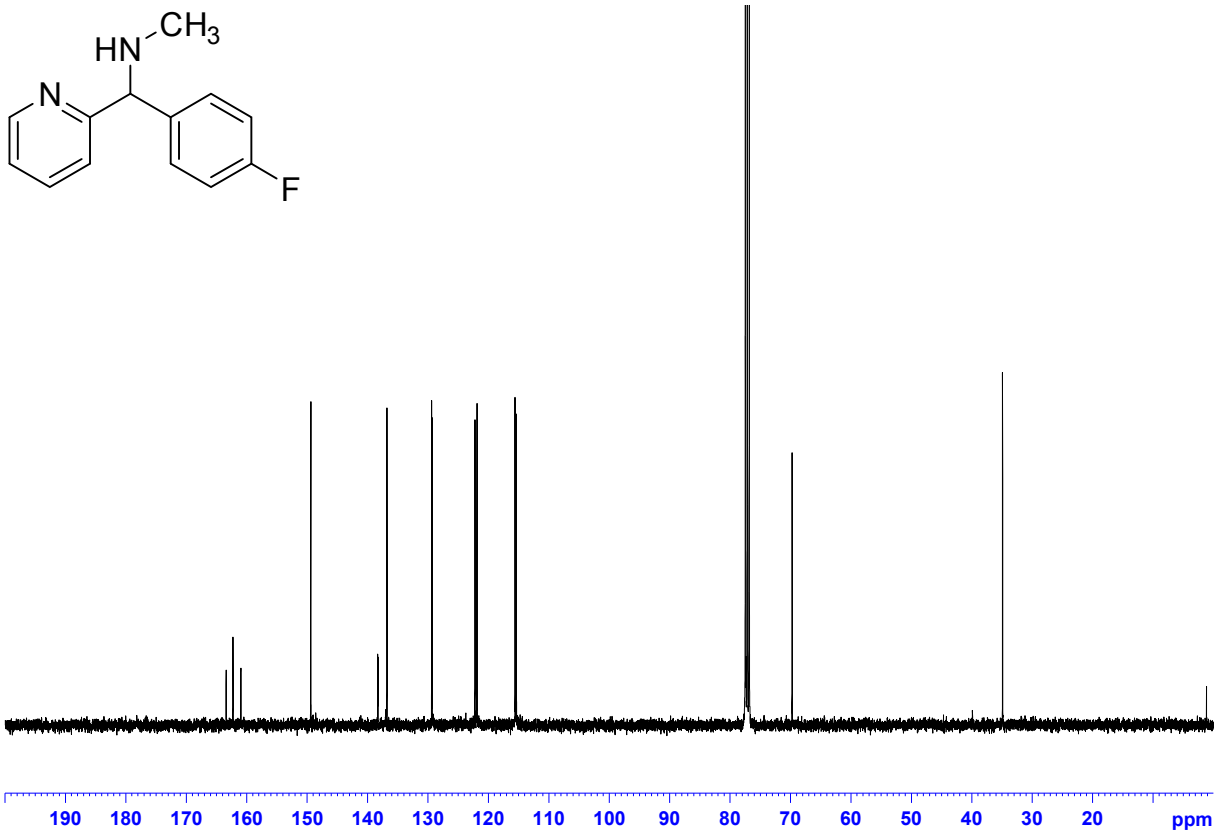
2f ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)



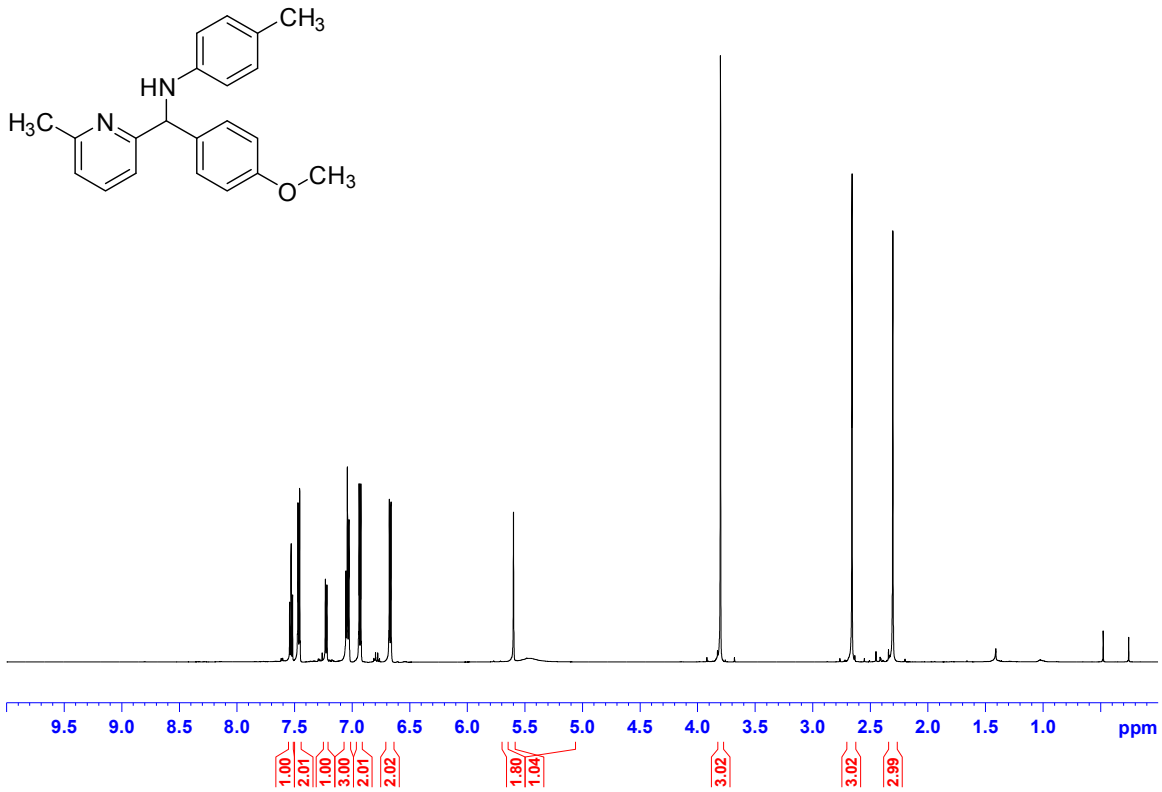
2g (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



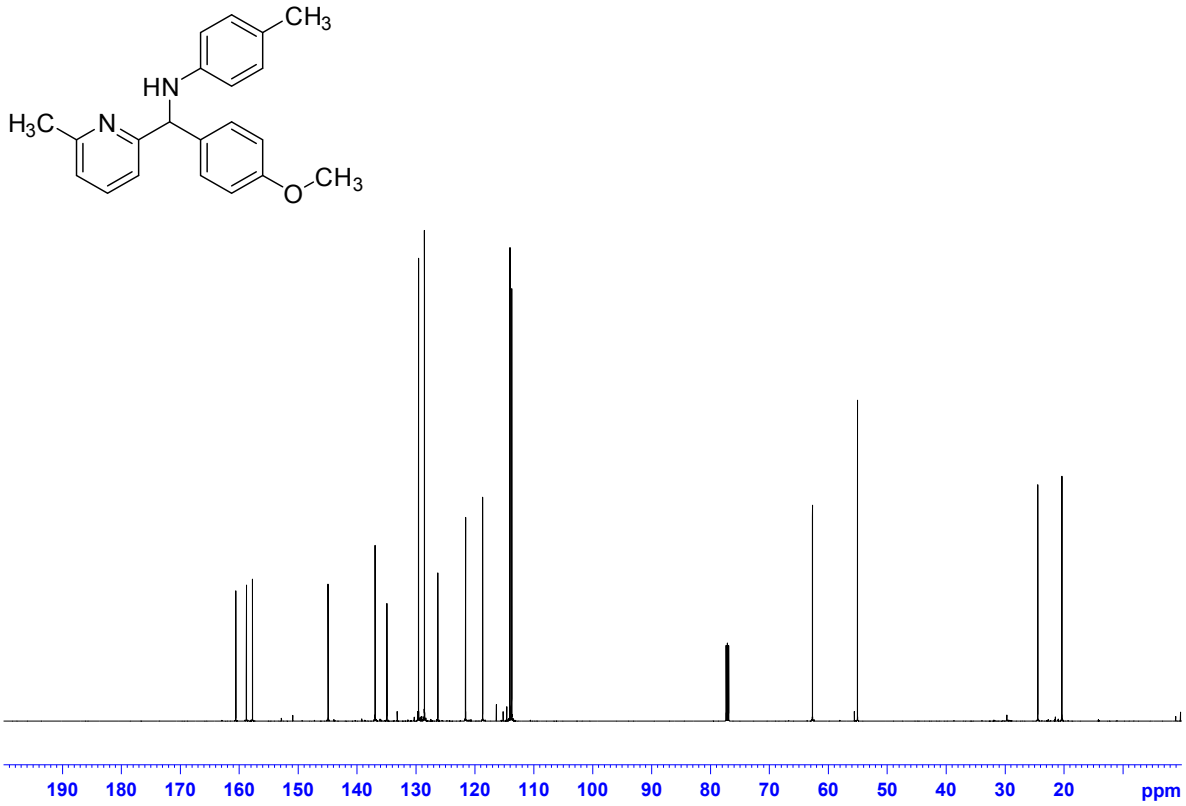
2g ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 295 K)



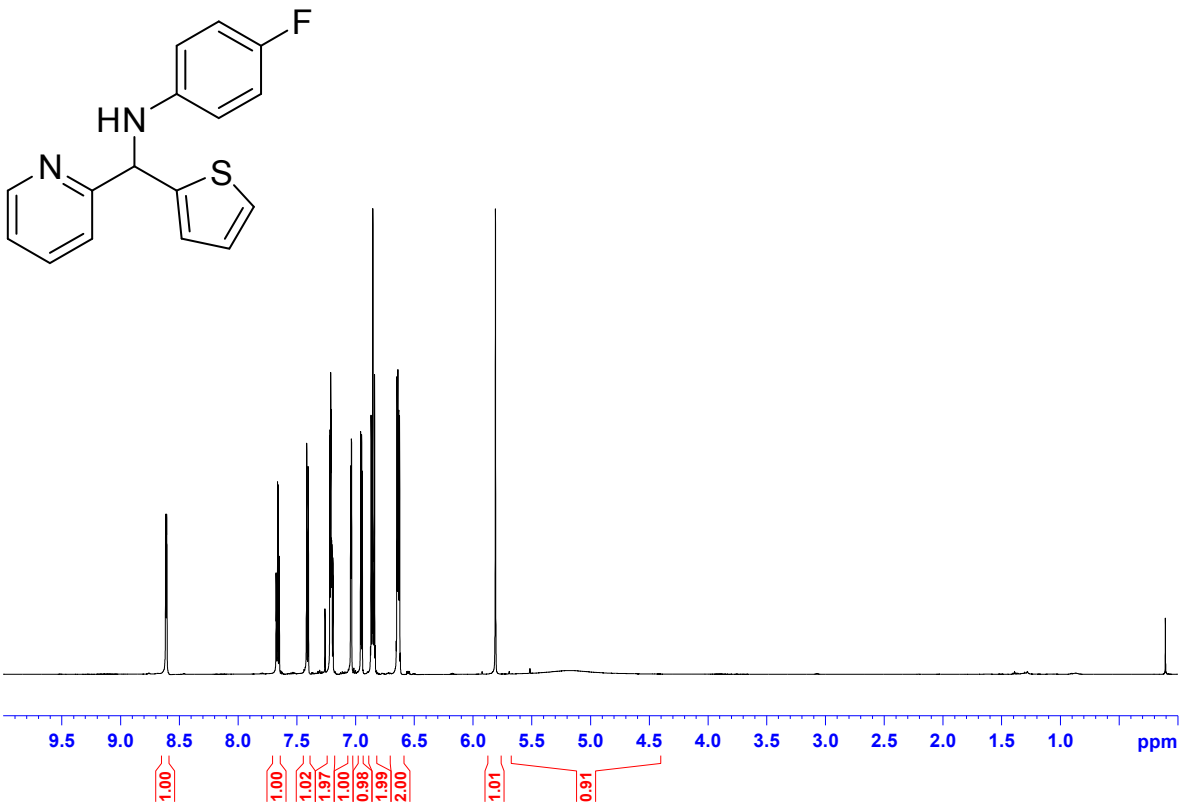
2h (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



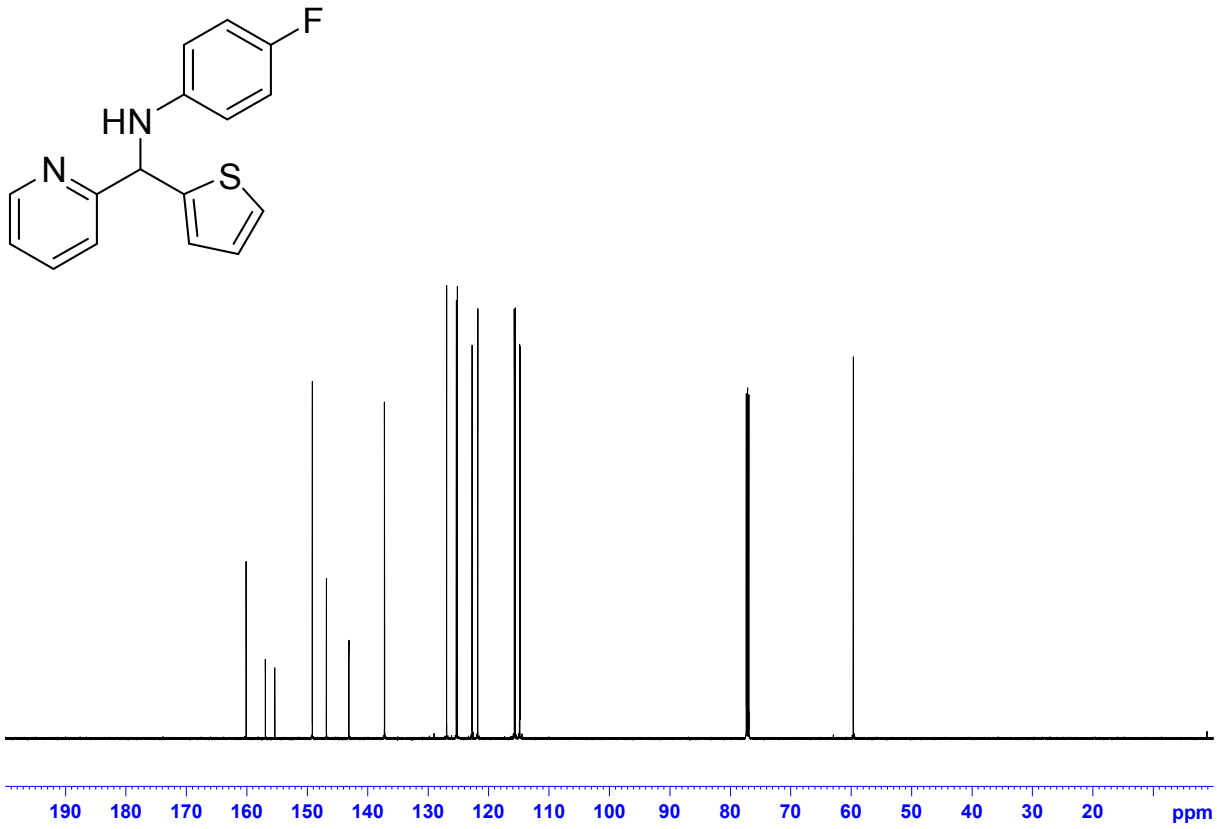
2h ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



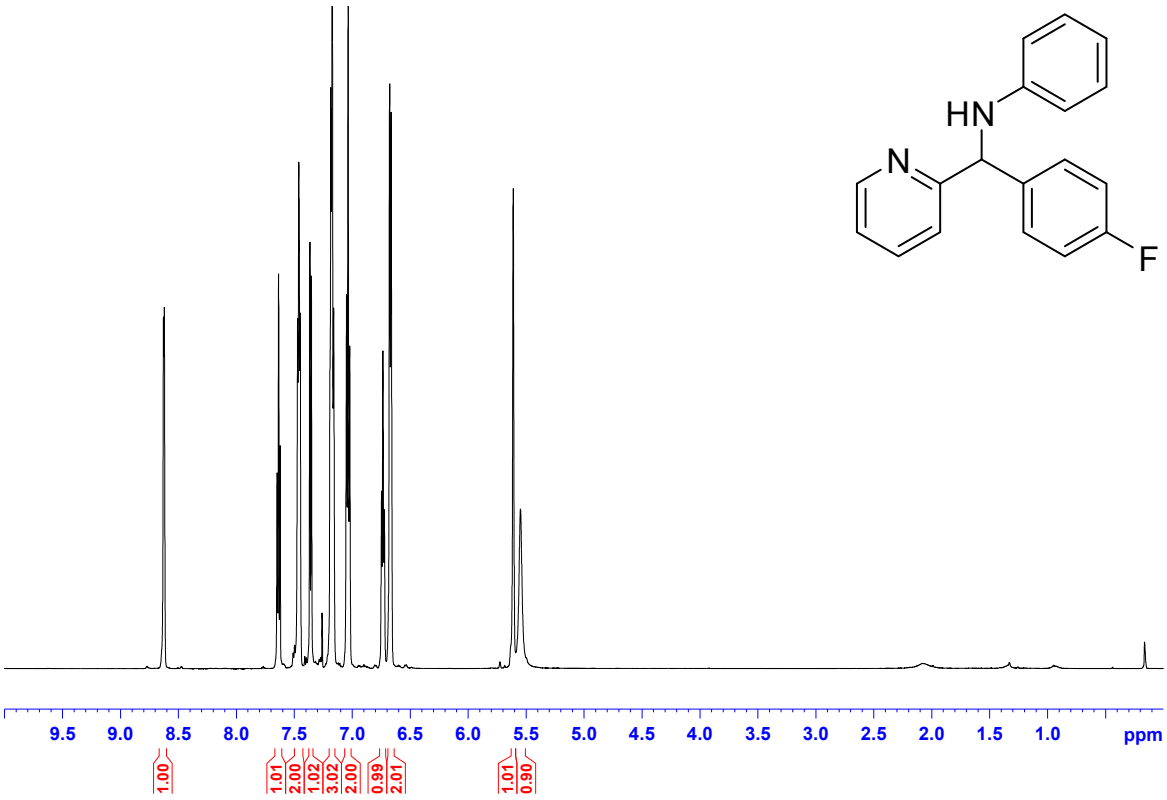
2i (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



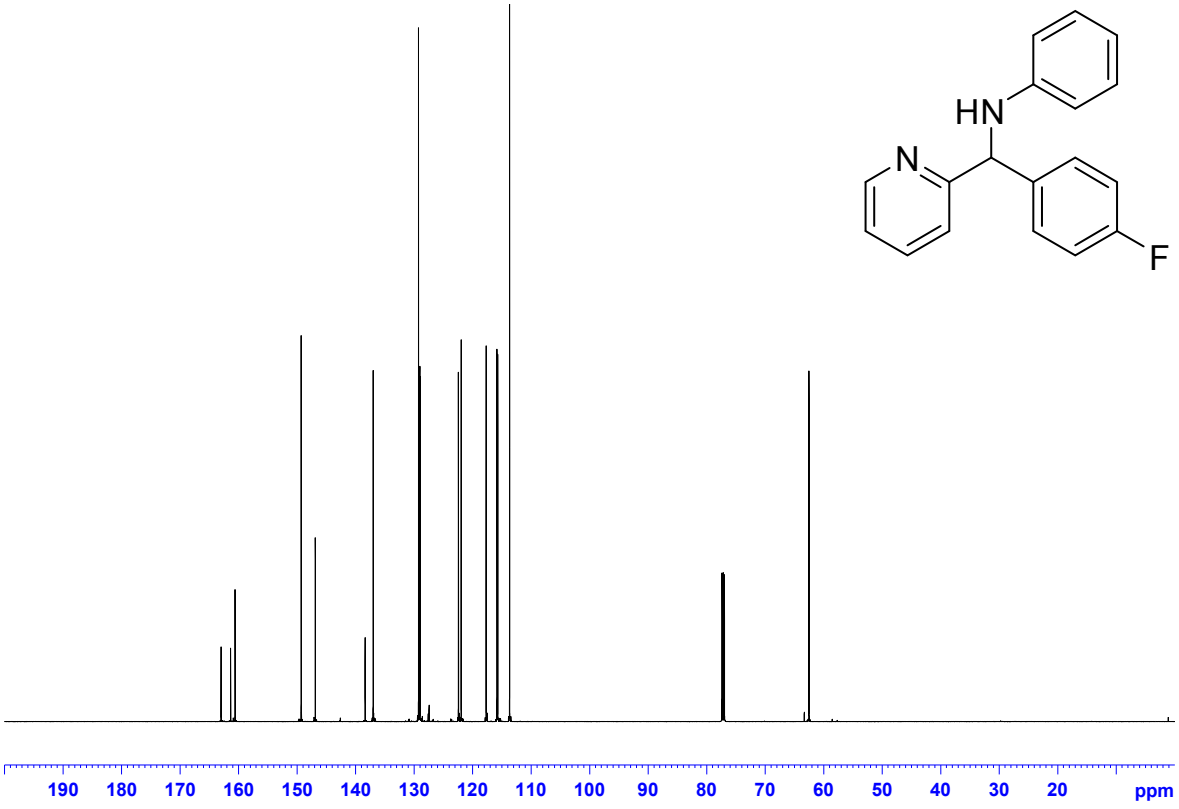
2i ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 298 K)



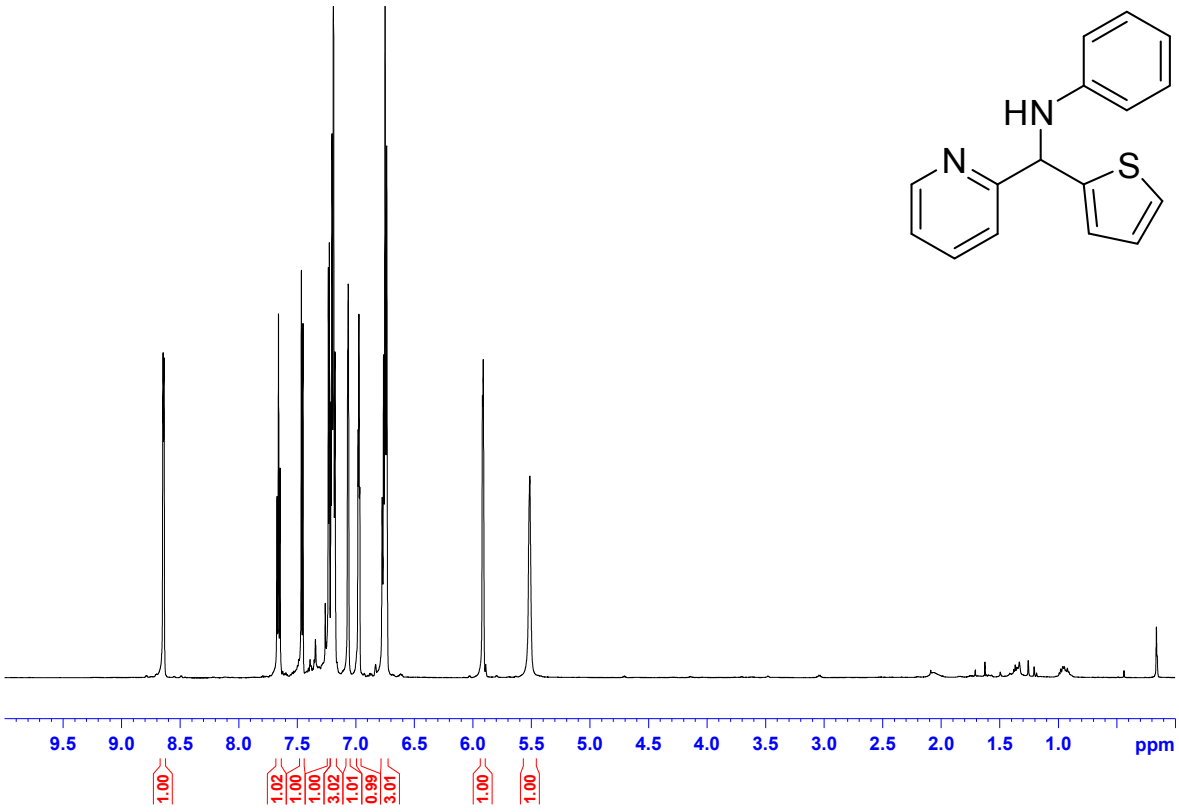
2j (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



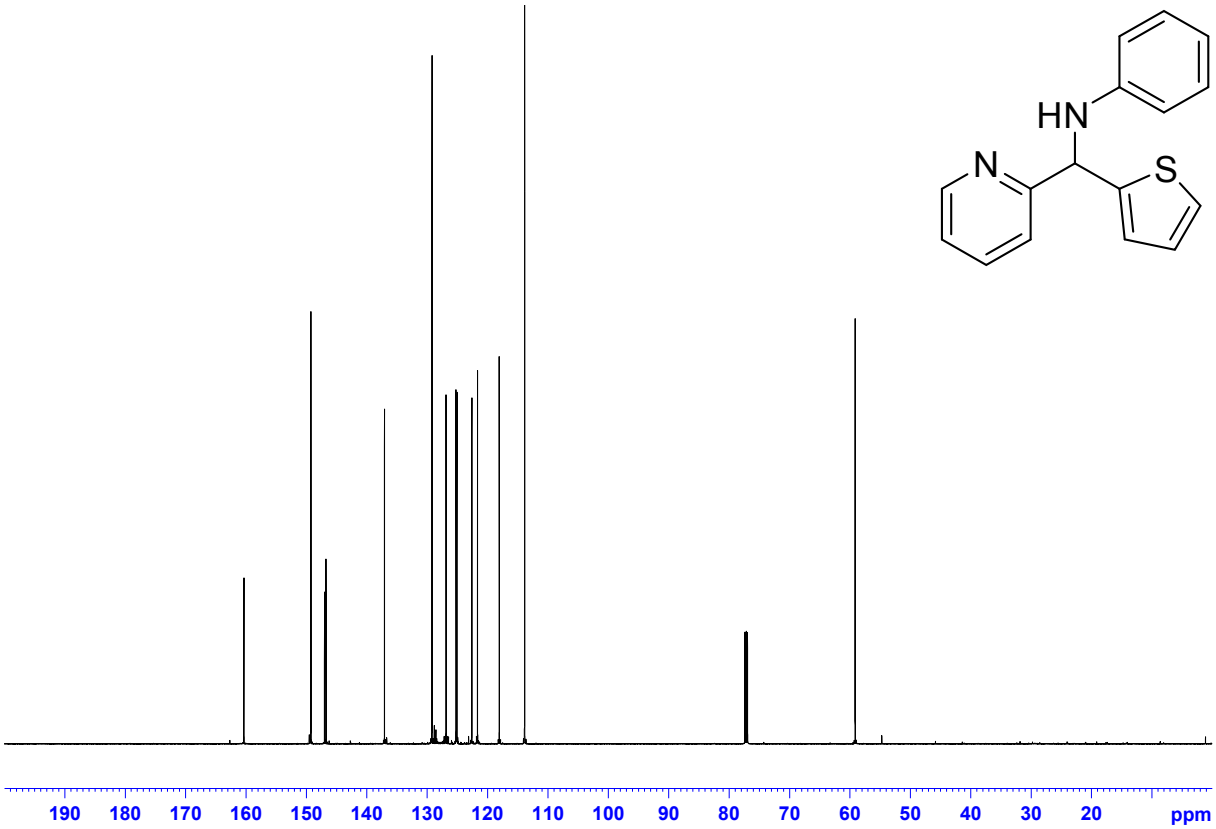
2j ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



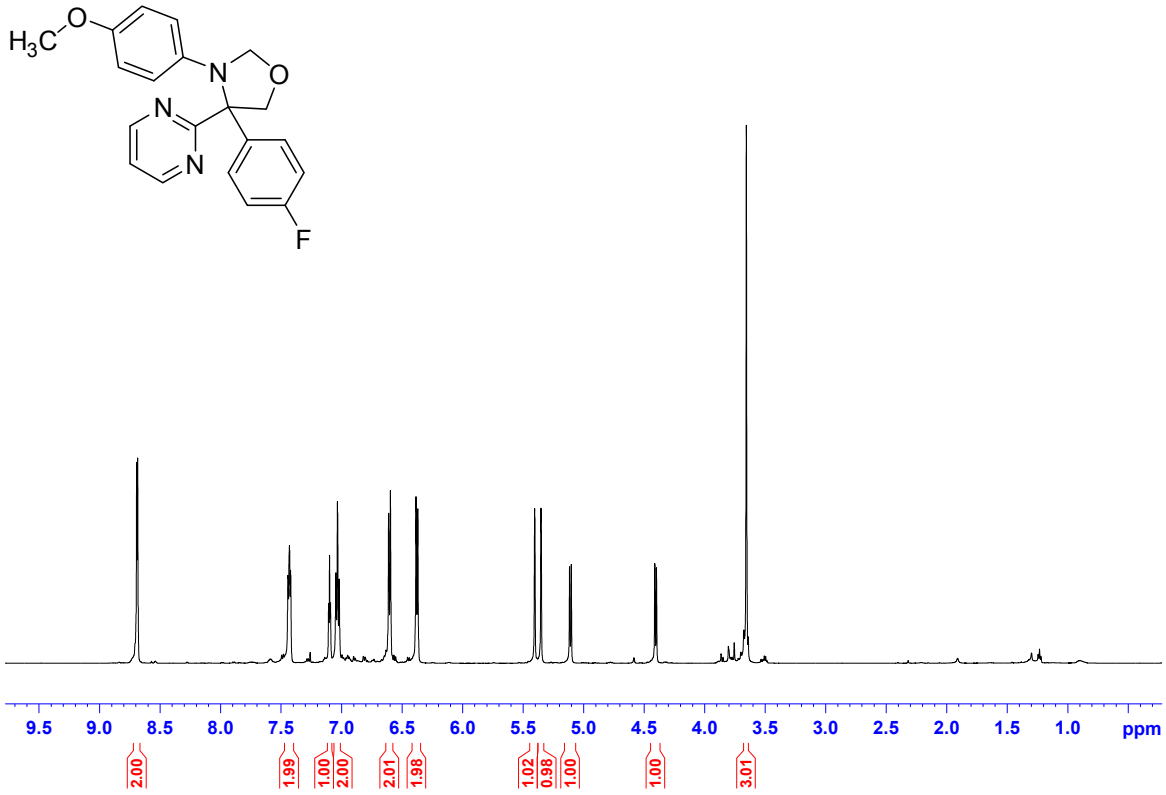
2k (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



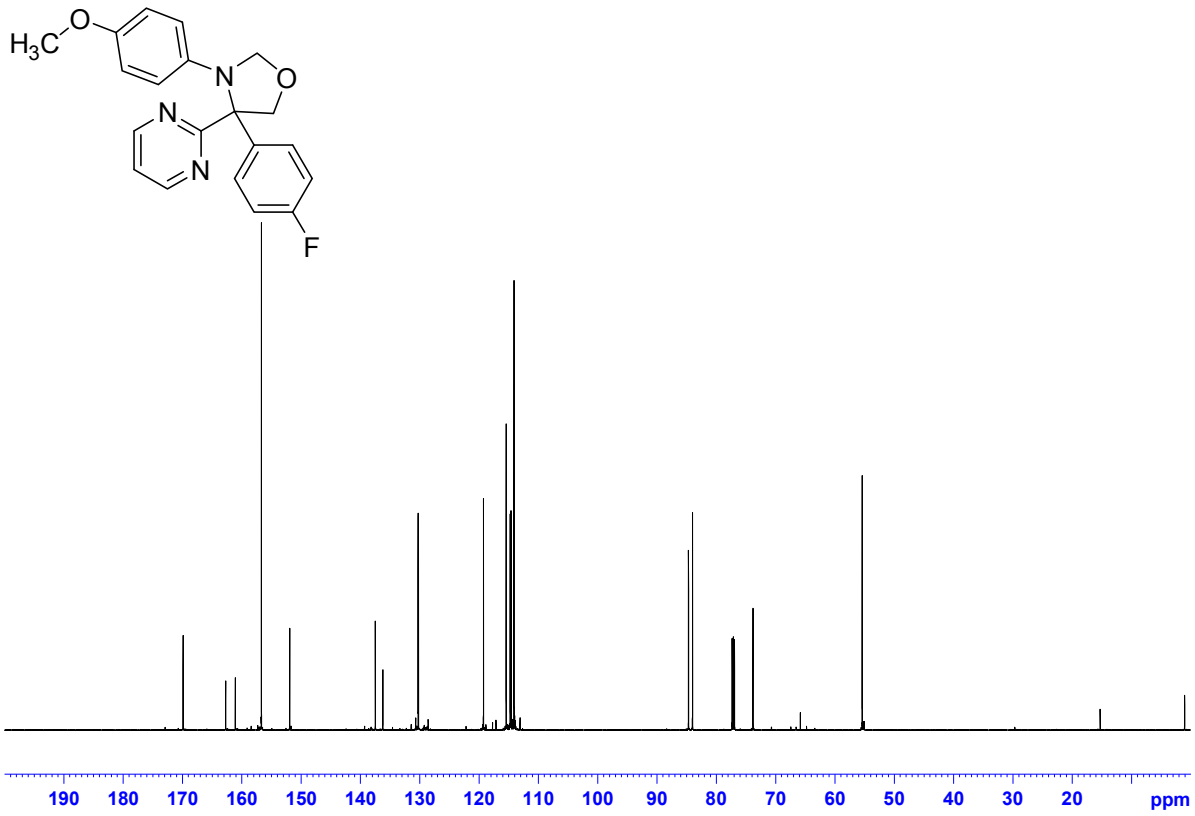
2k ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



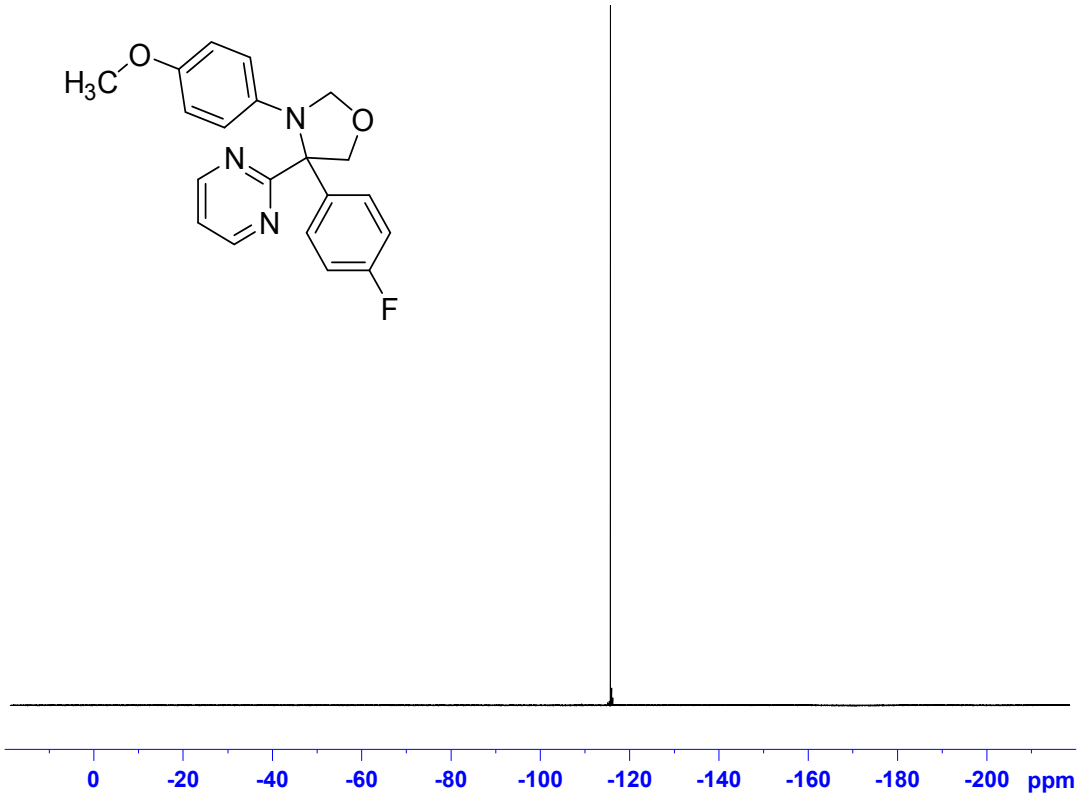
5a (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



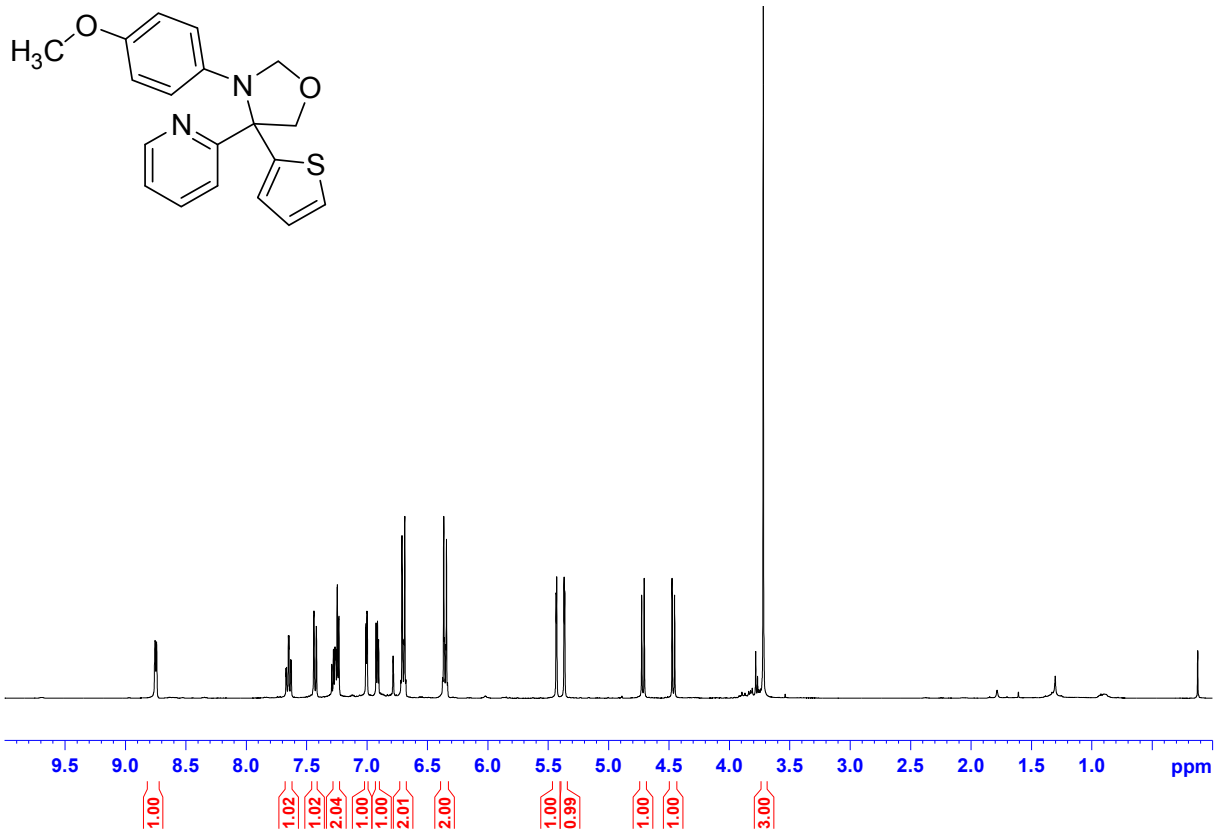
5a ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



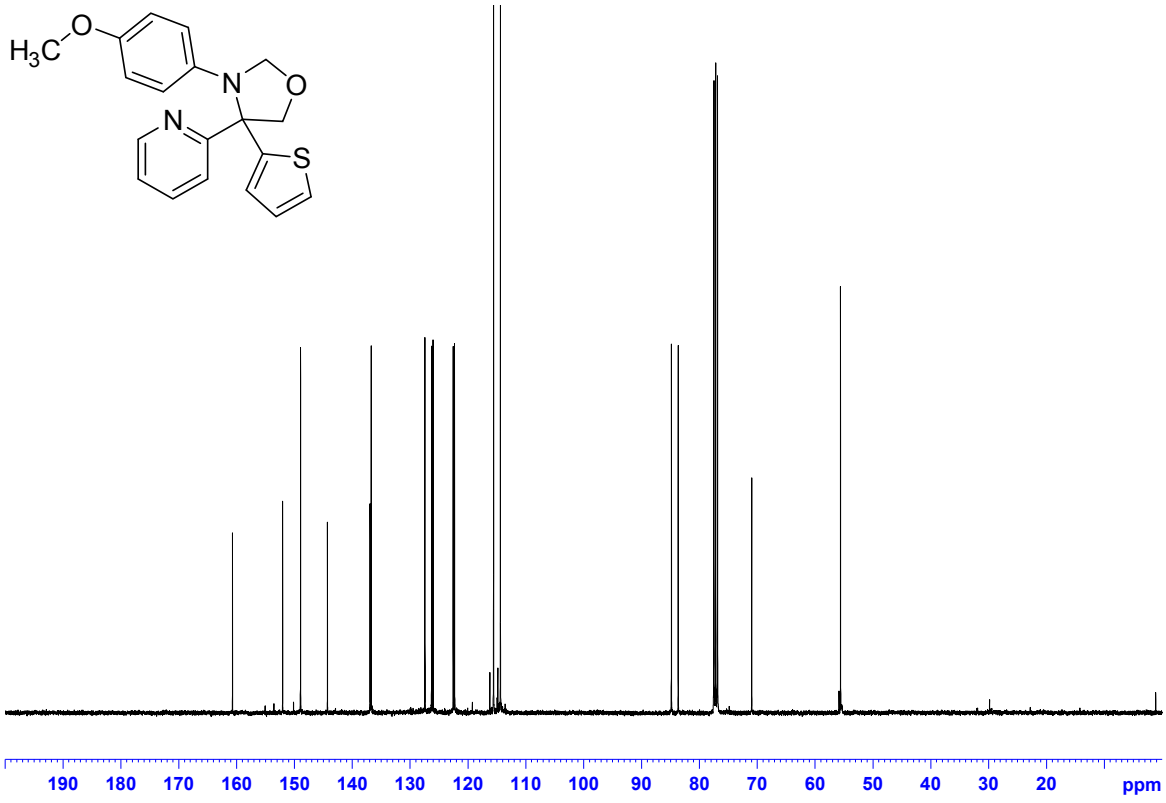
5a ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 298 K)



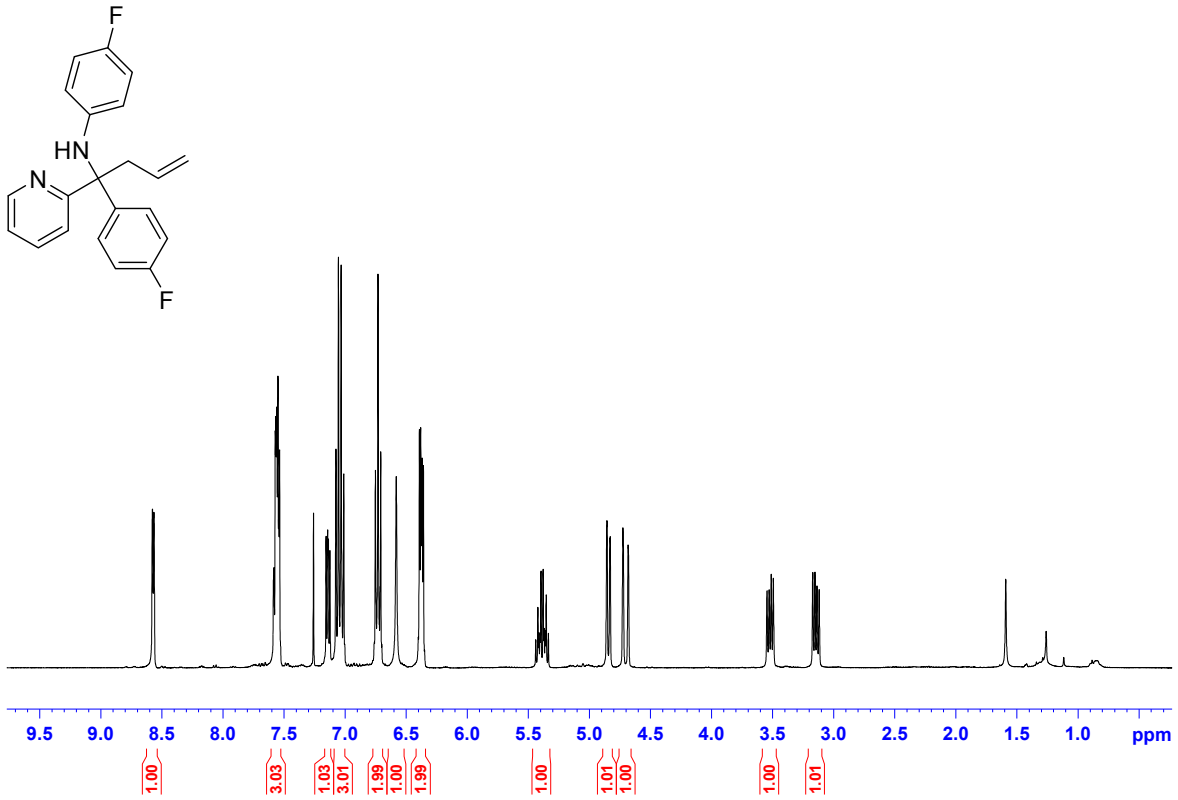
5b (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



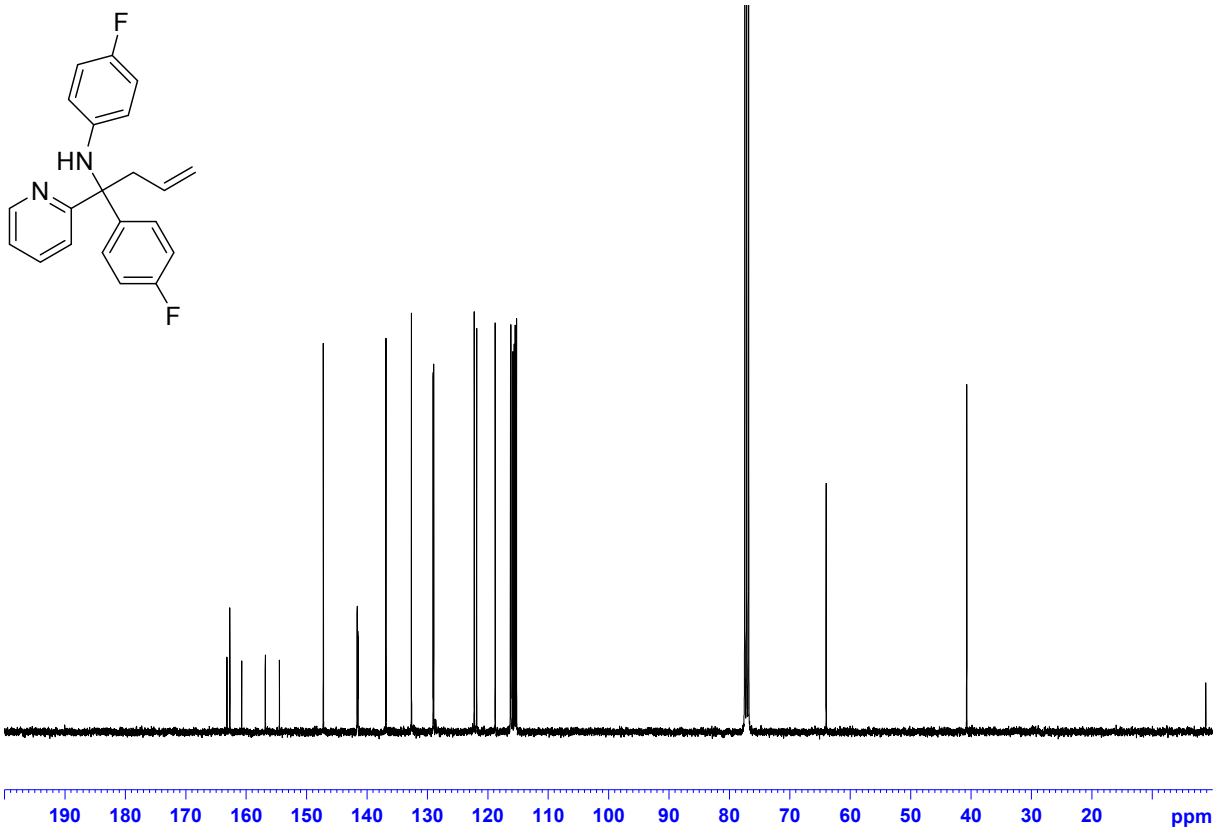
5b (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 295 K)



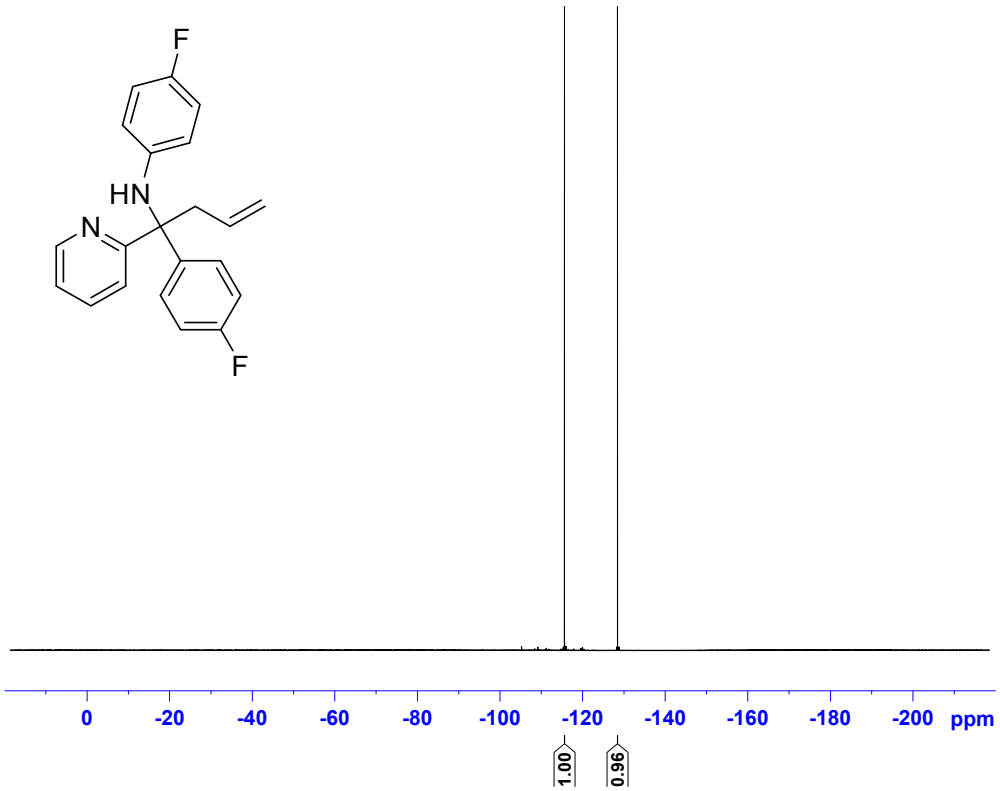
6a (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



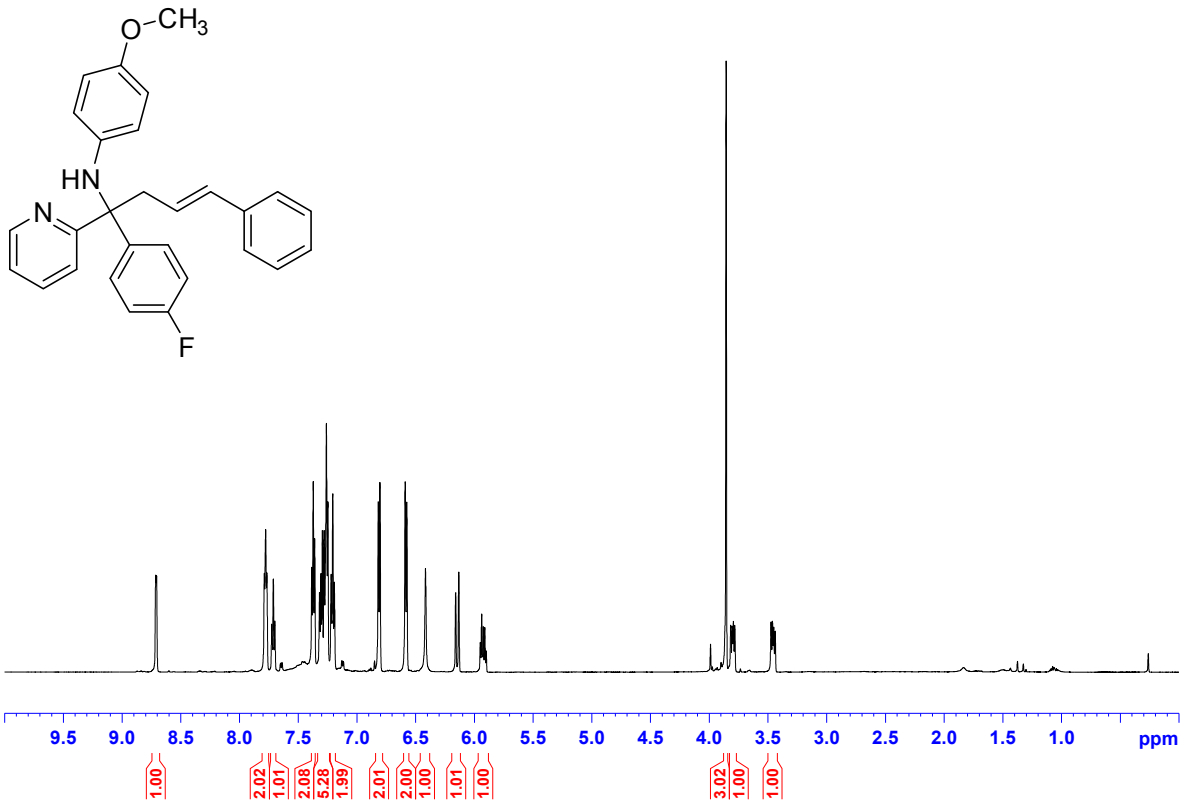
6a ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 295 K)



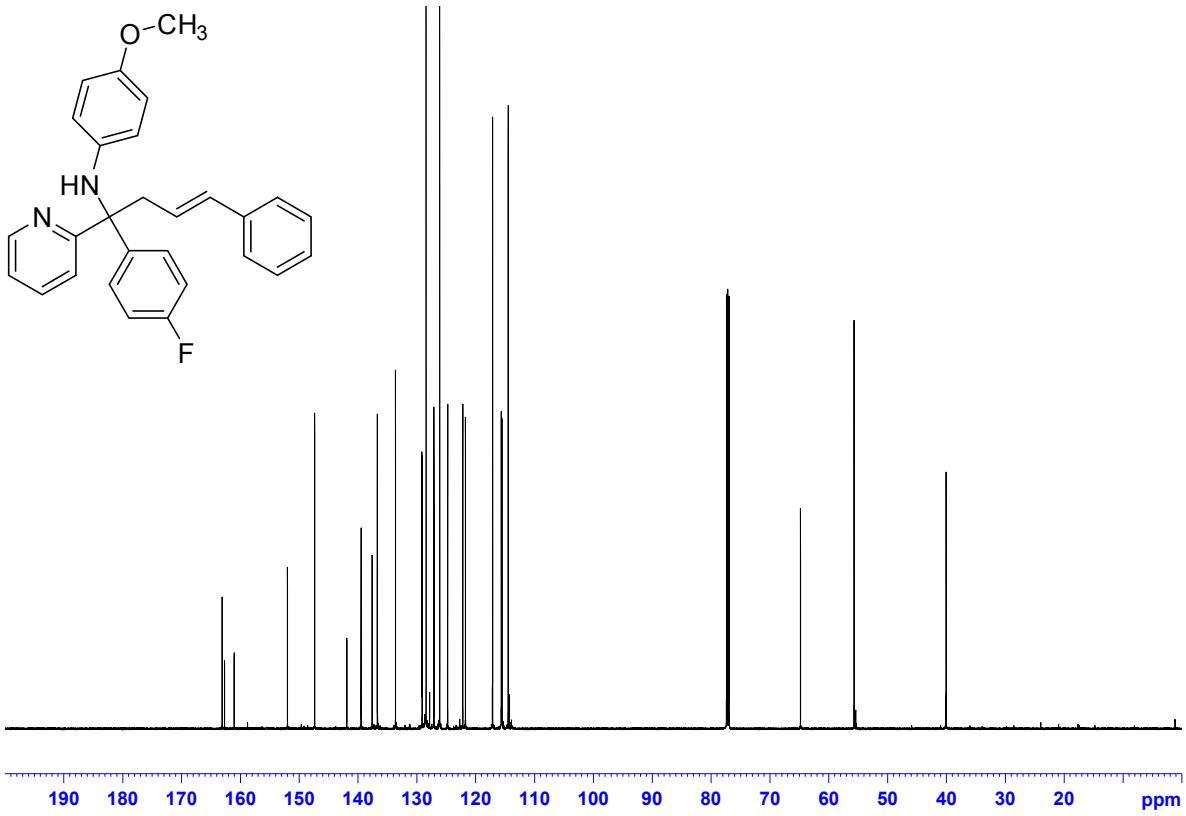
6a ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.37 MHz, 295 K)



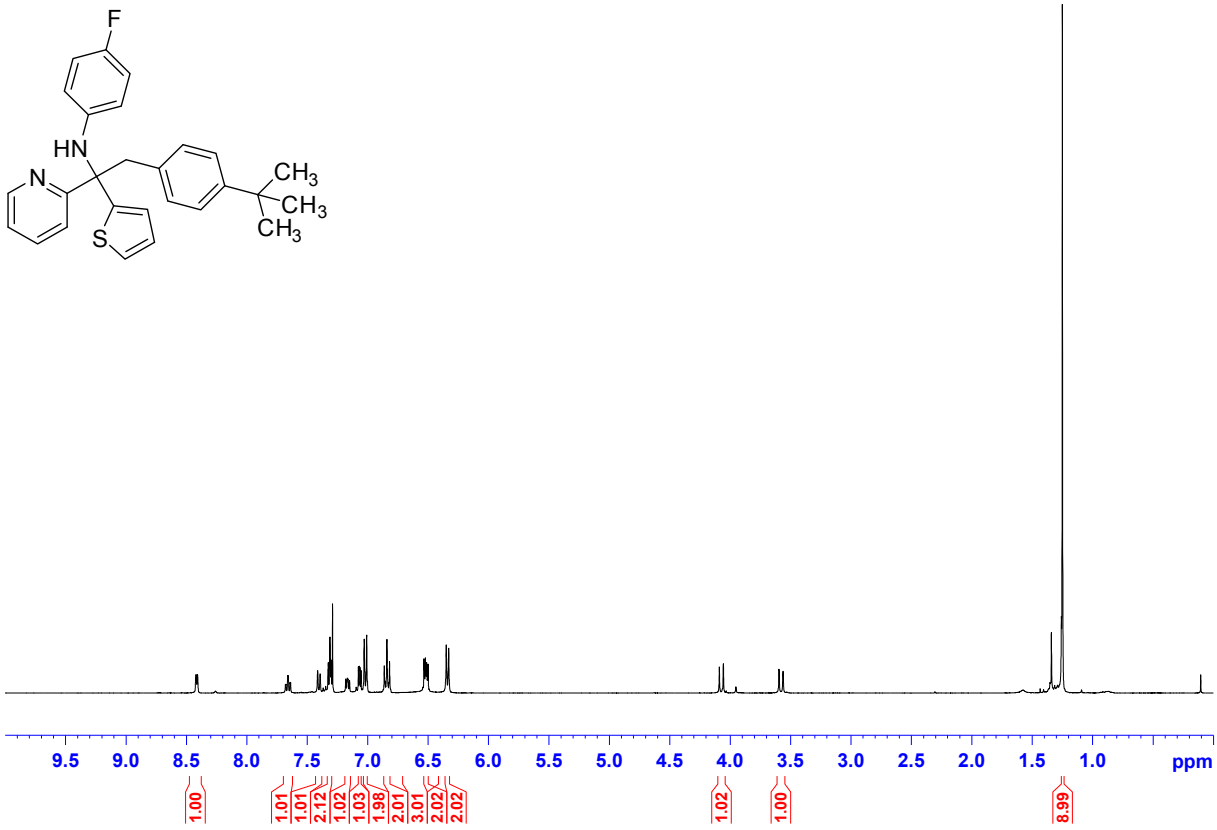
6b (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



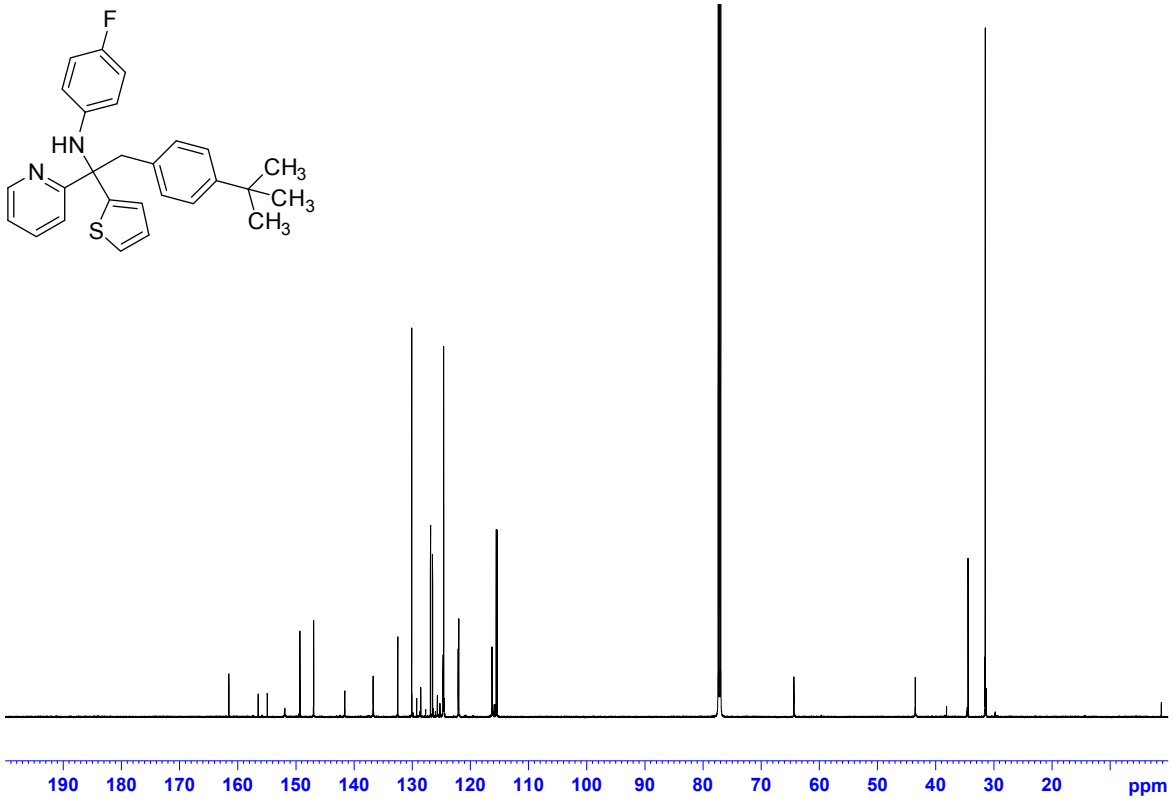
6b ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



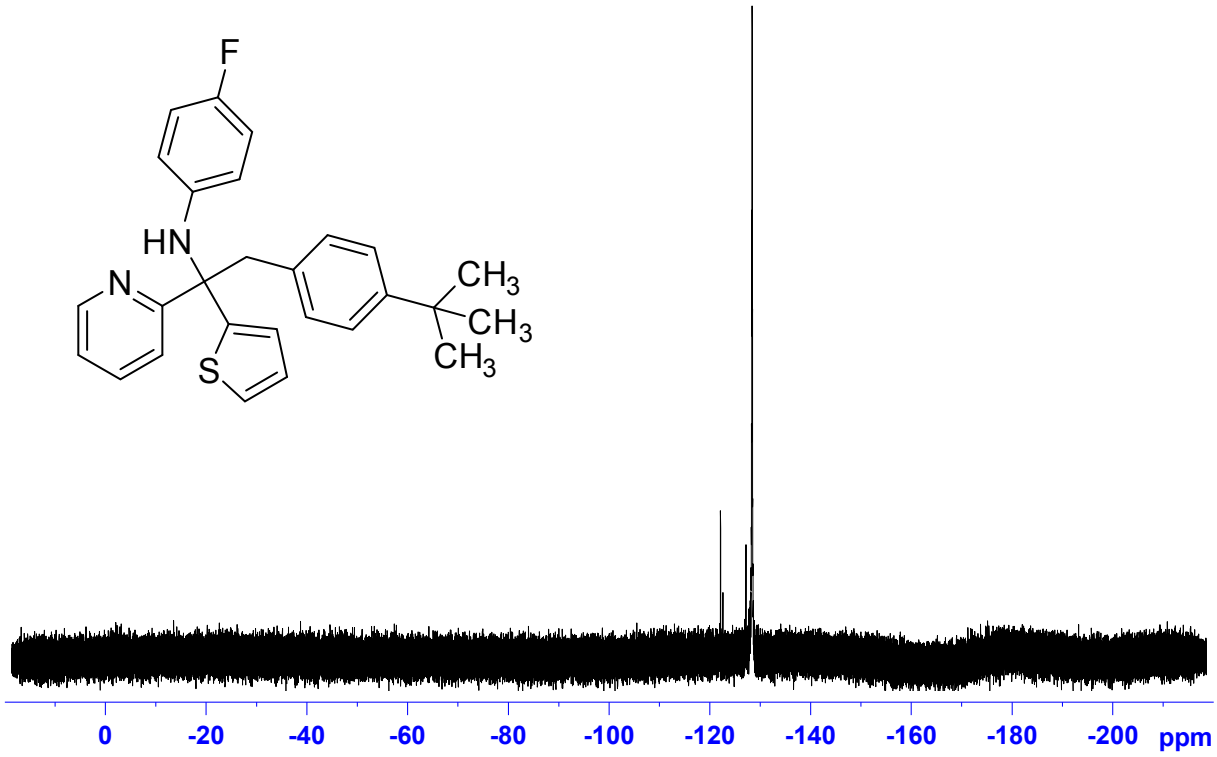
6c (^{1}H NMR, $CDCl_3$, 399.89 MHz, 296 K)



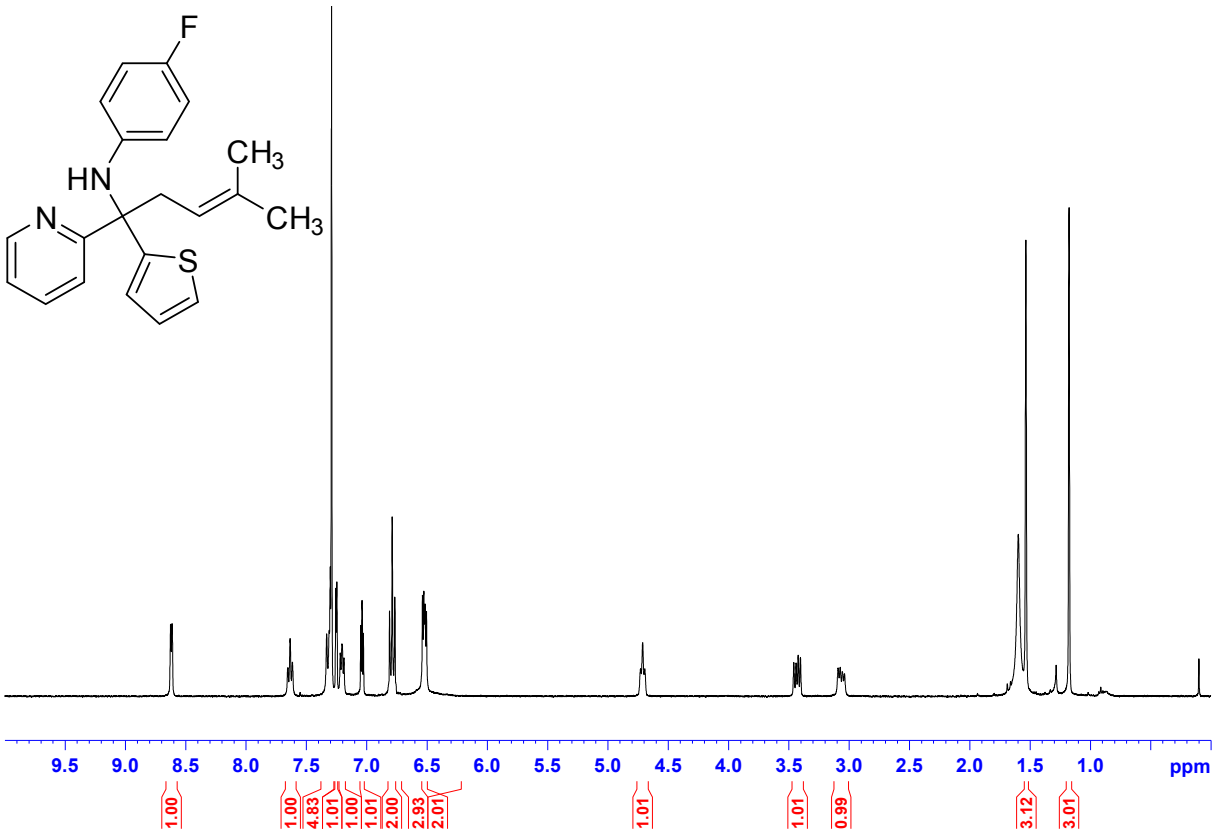
6c ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)



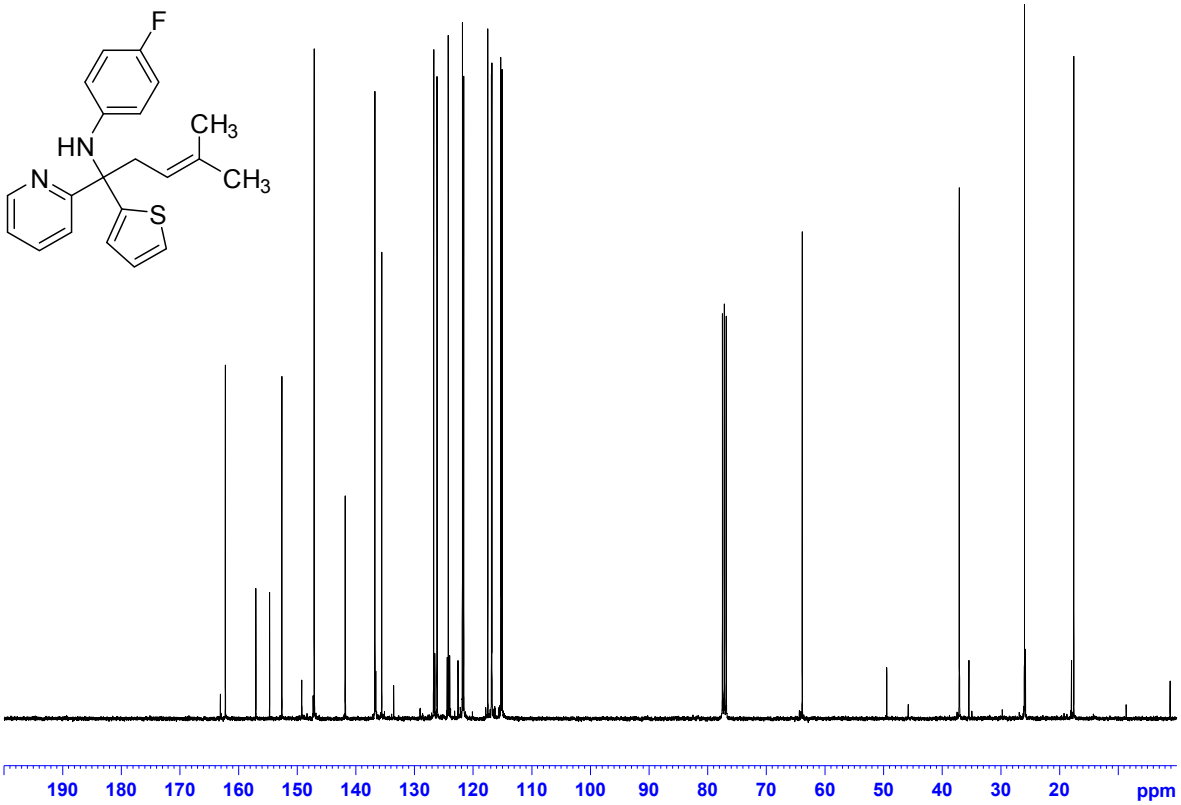
6c ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 296 K)



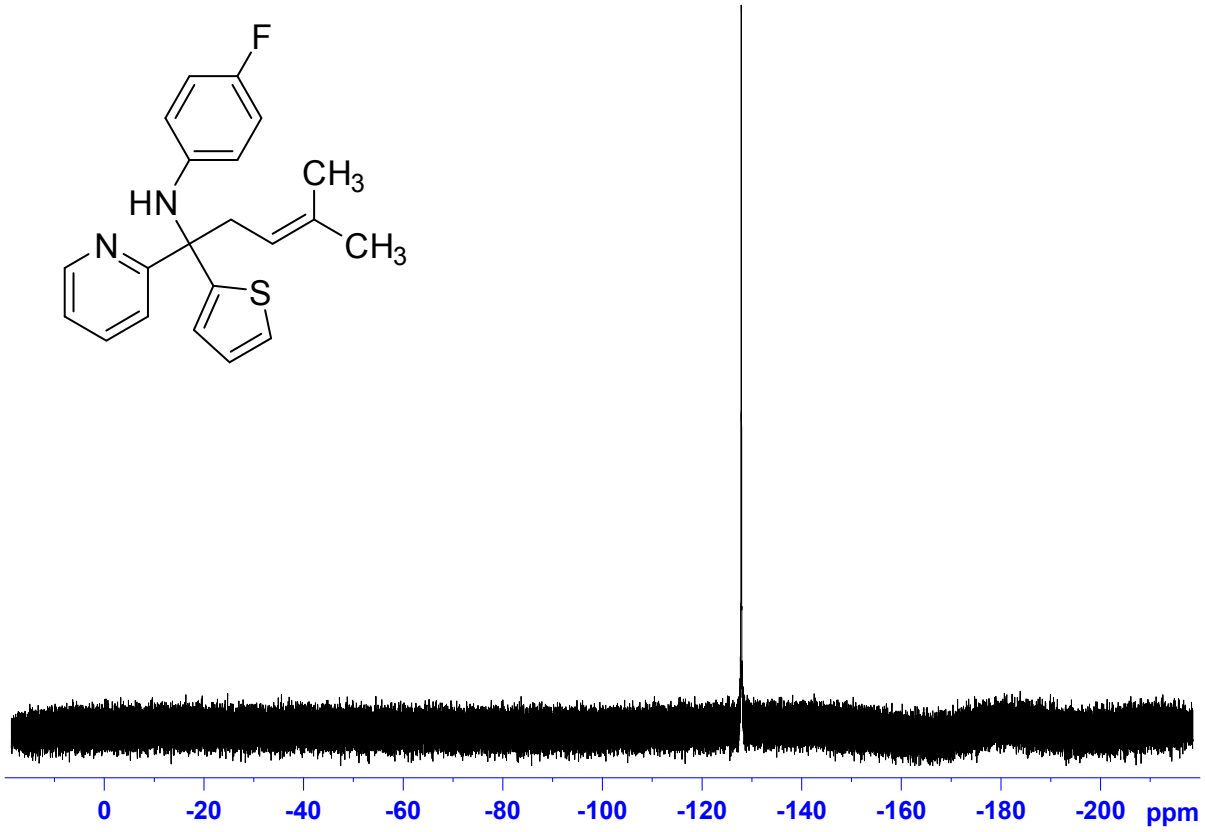
7a (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



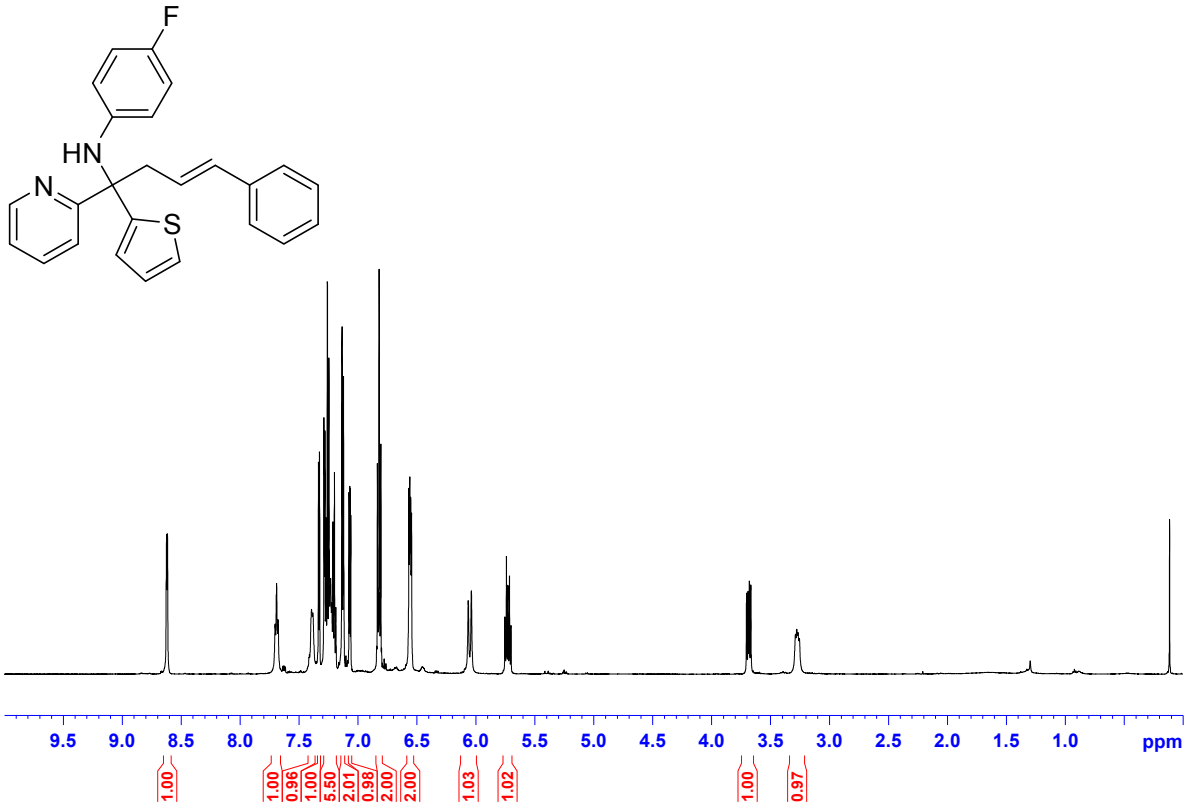
7a (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 295 K)



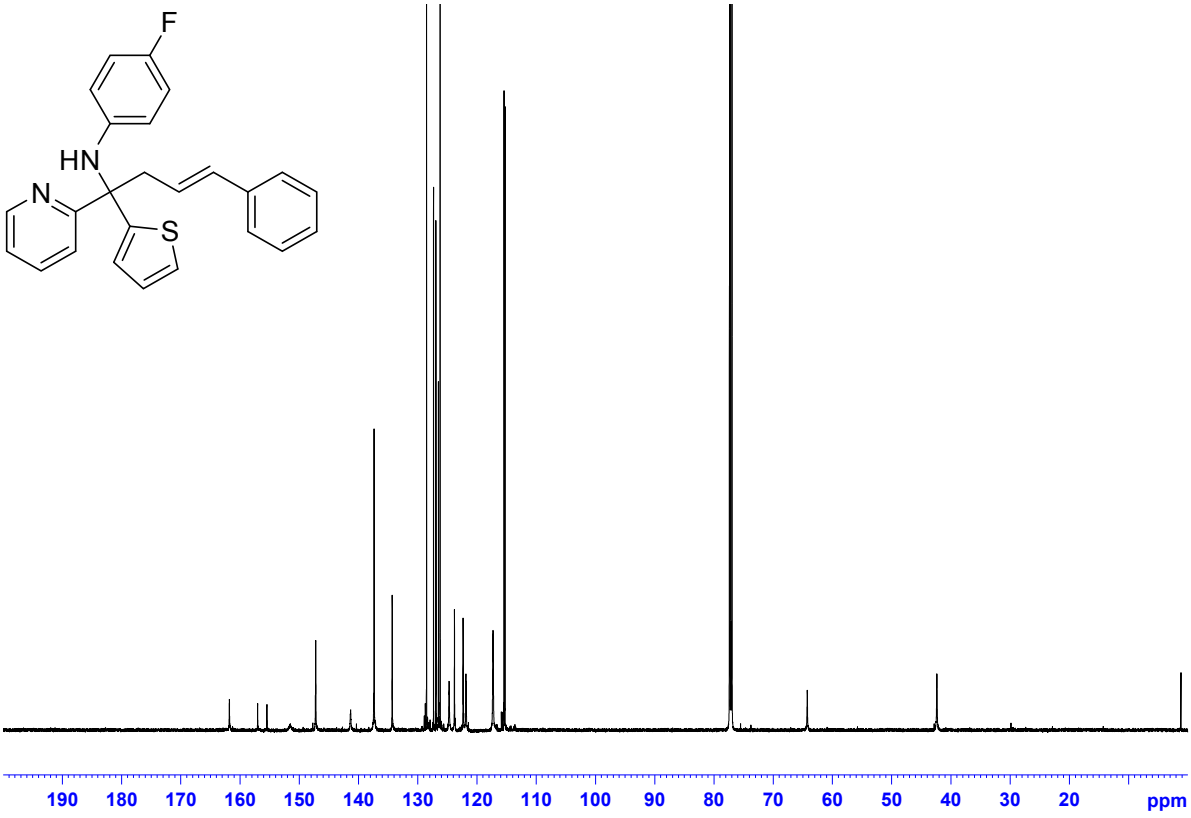
7a ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)



7b (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)

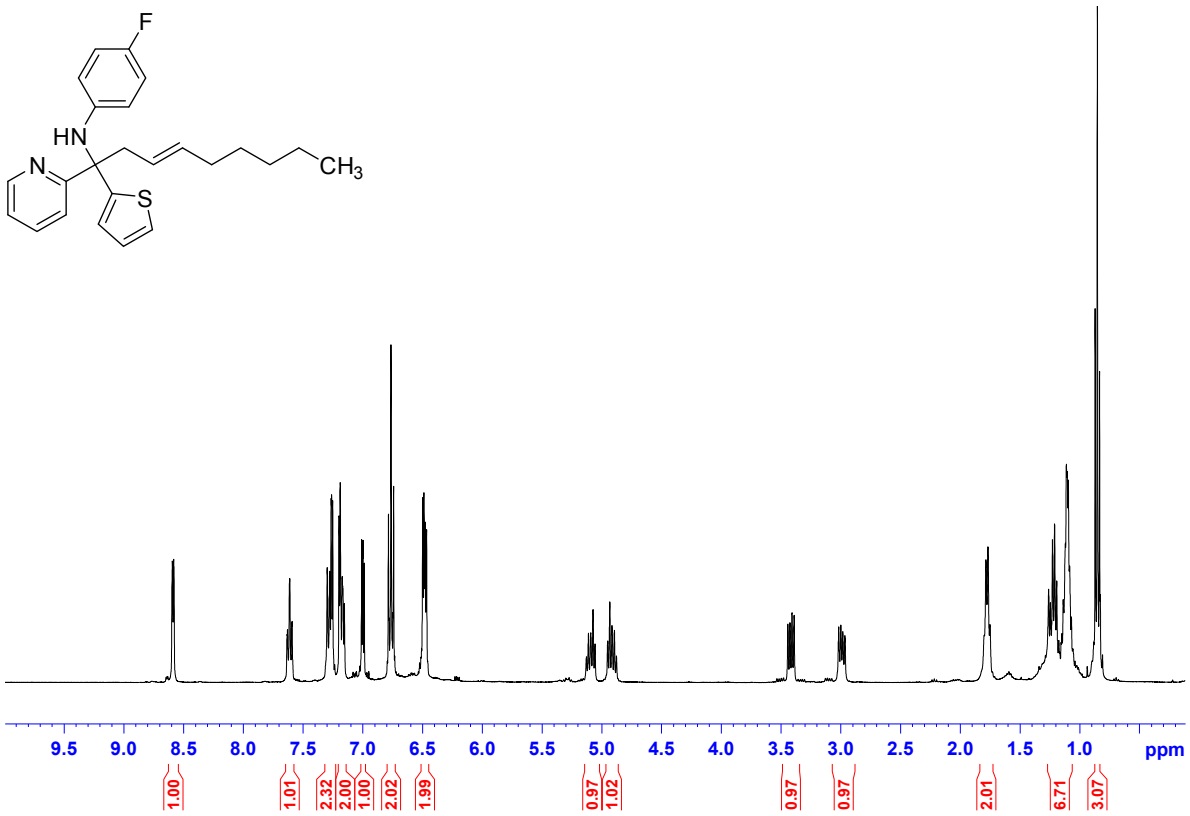


7b ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150.90 MHz, 295 K)

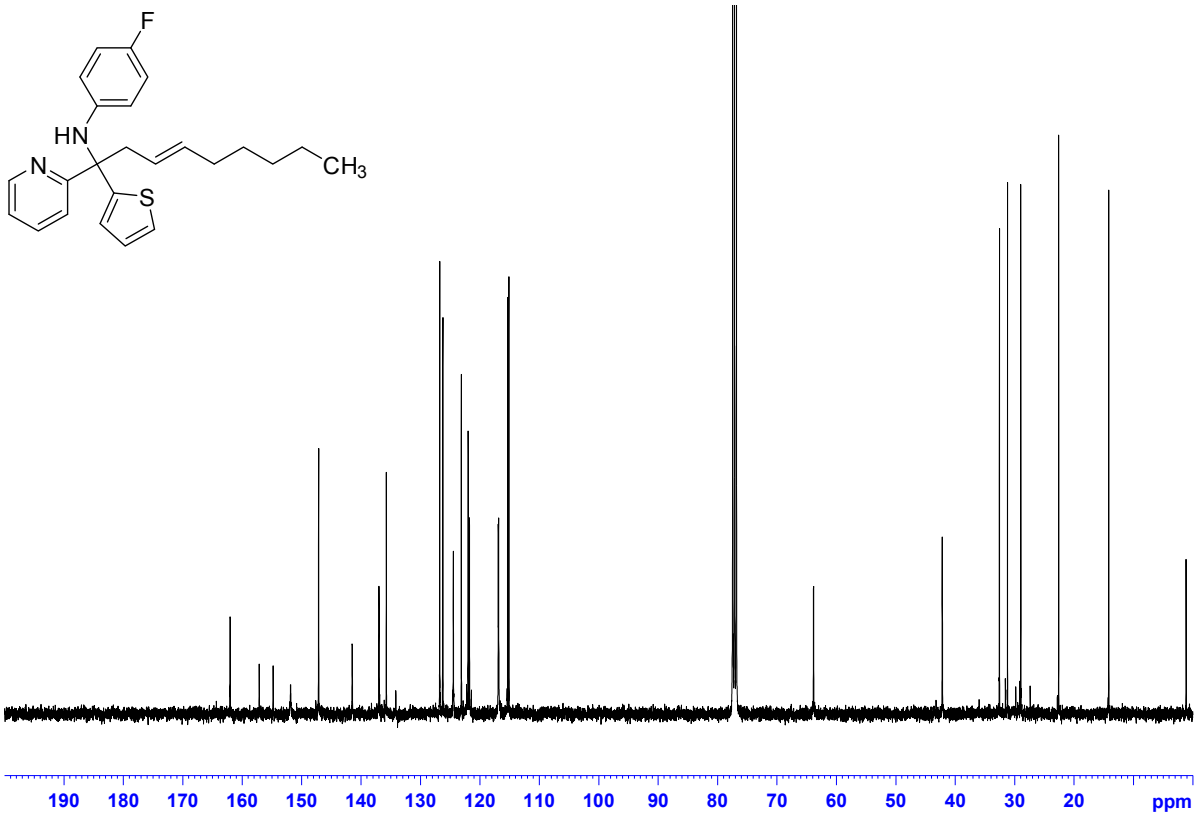


7b ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 295 K)

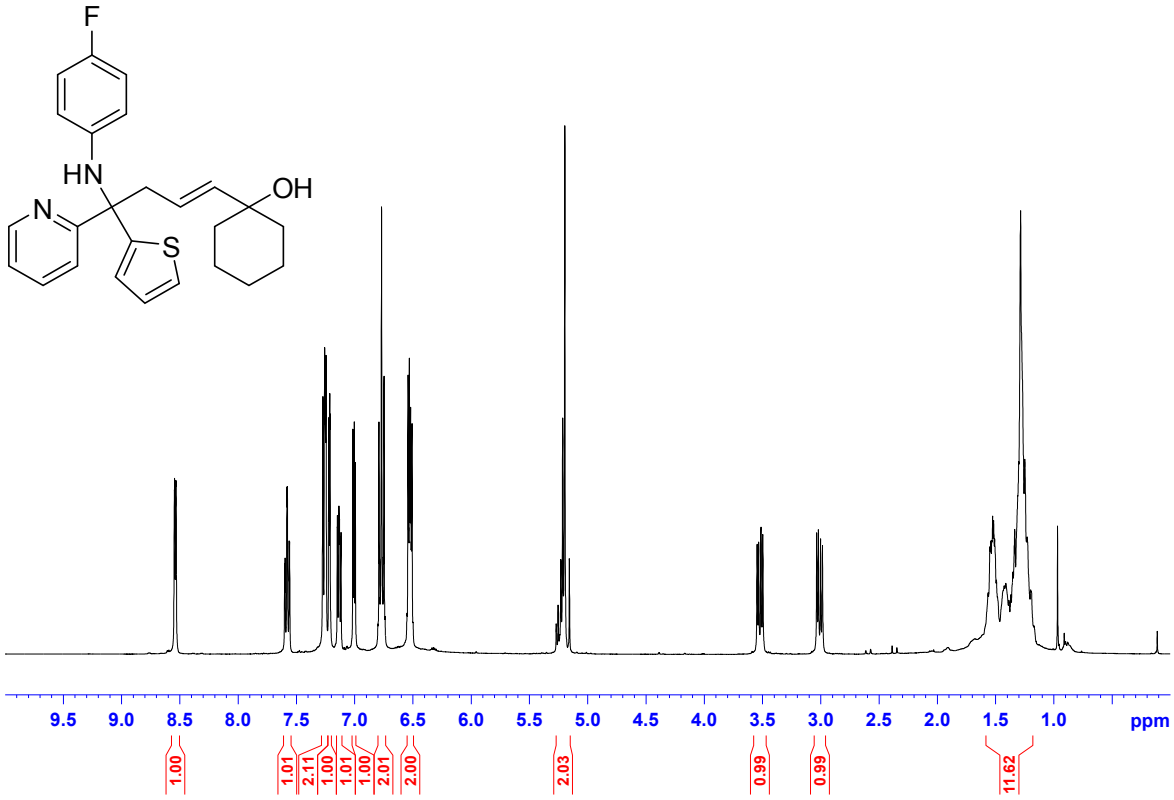
7c (^{1}H NMR, $CDCl_3$, 399.89 MHz, 295 K)



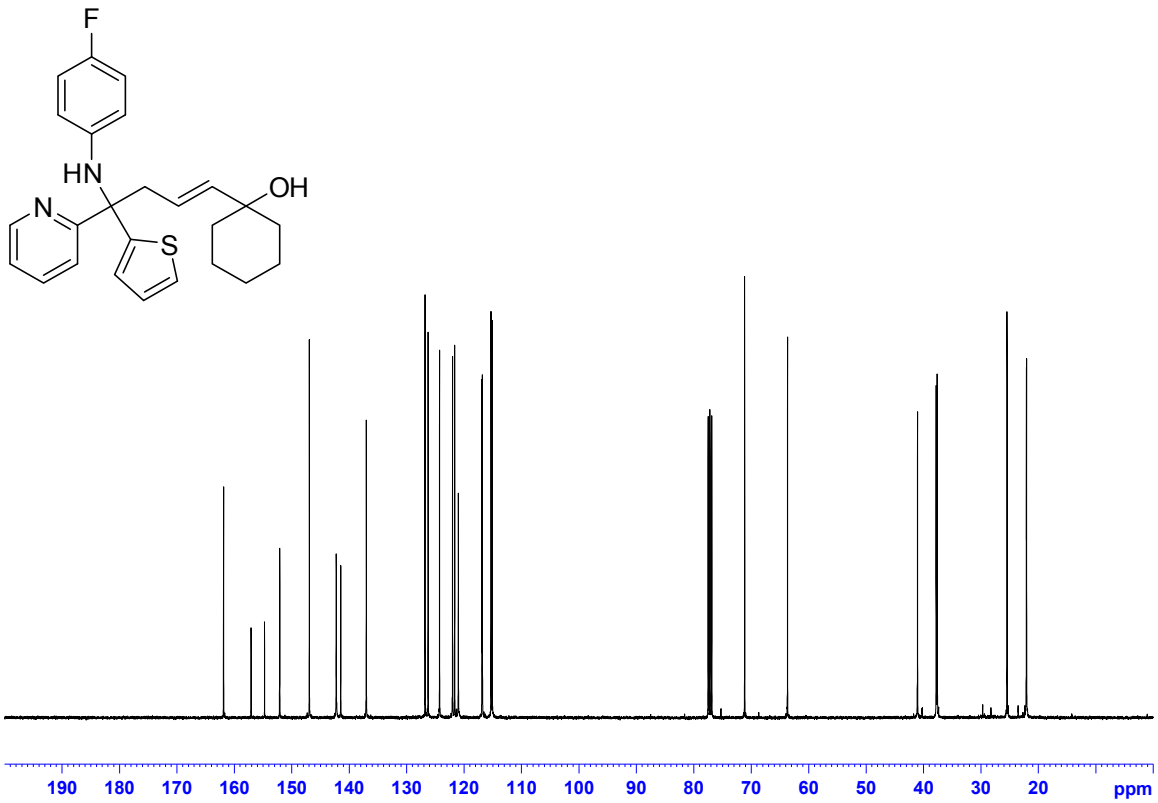
7c (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 295 K)



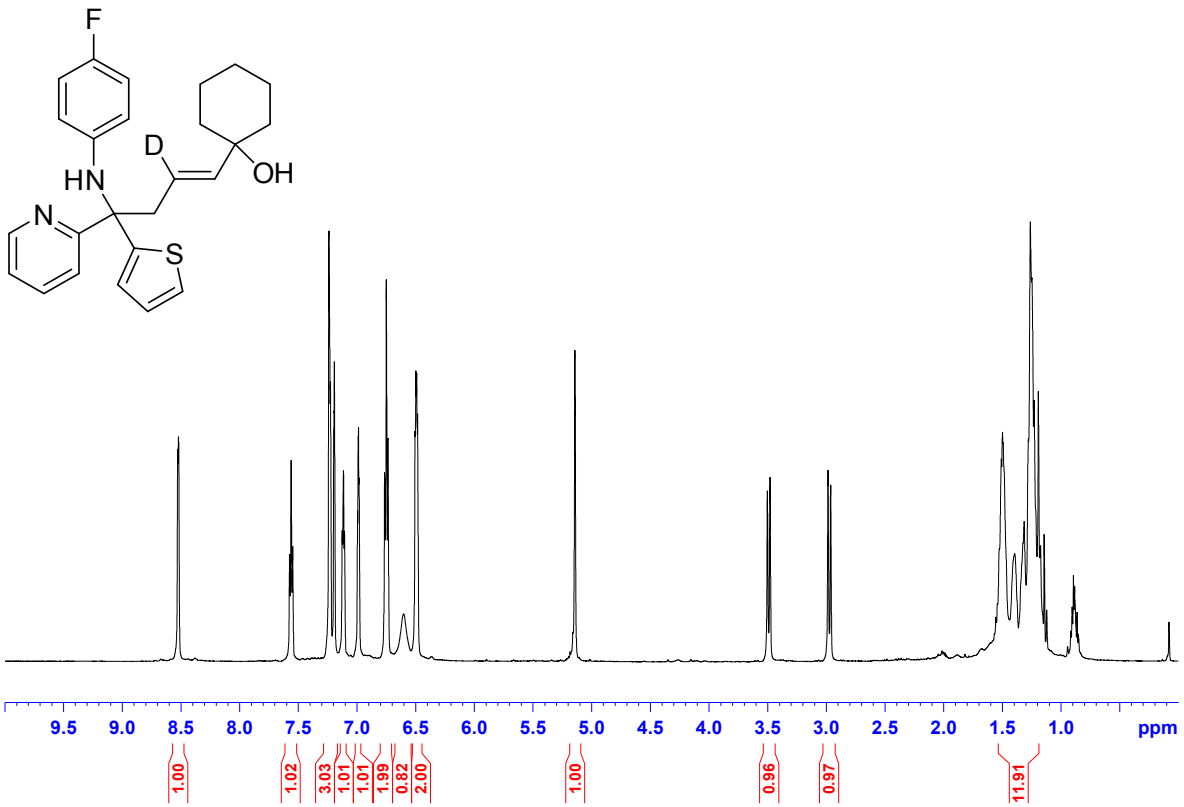
8a (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



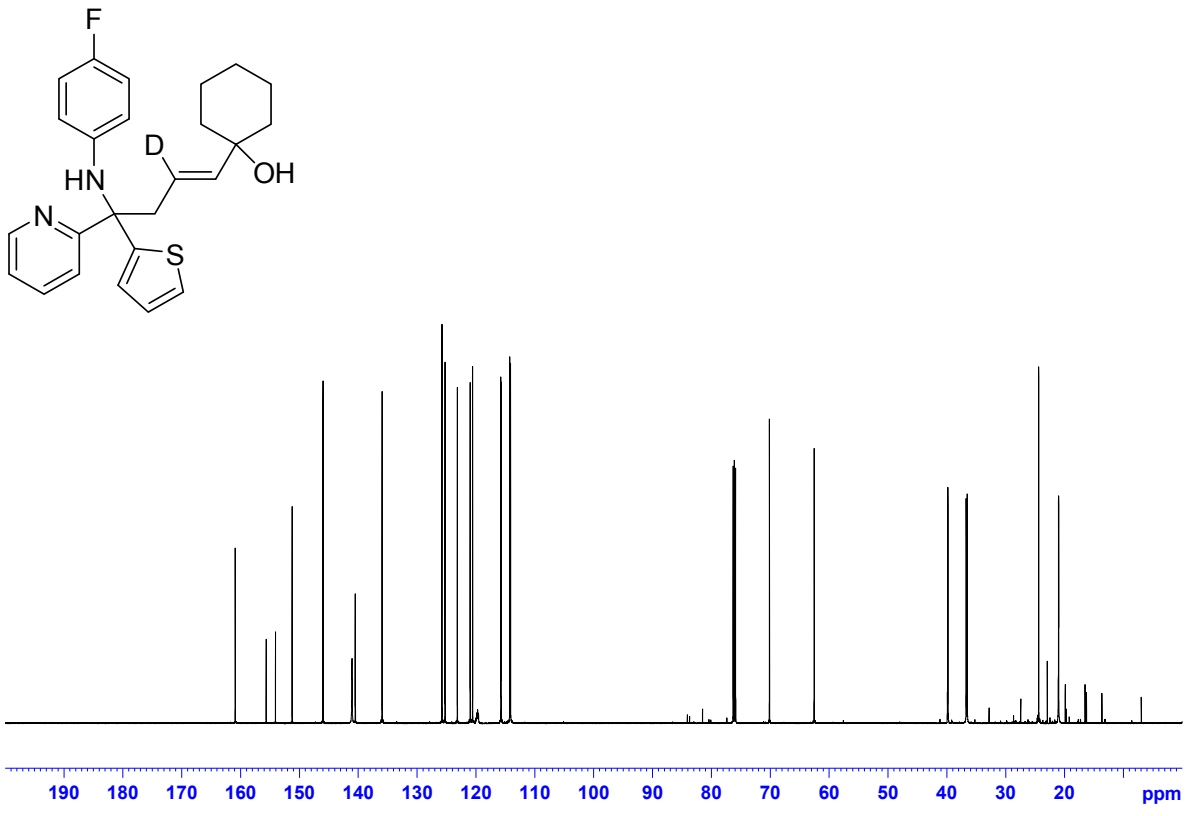
8a (^{13}C{^{1}H} NMR, $CDCl_3$, 100.55 MHz, 299 K)



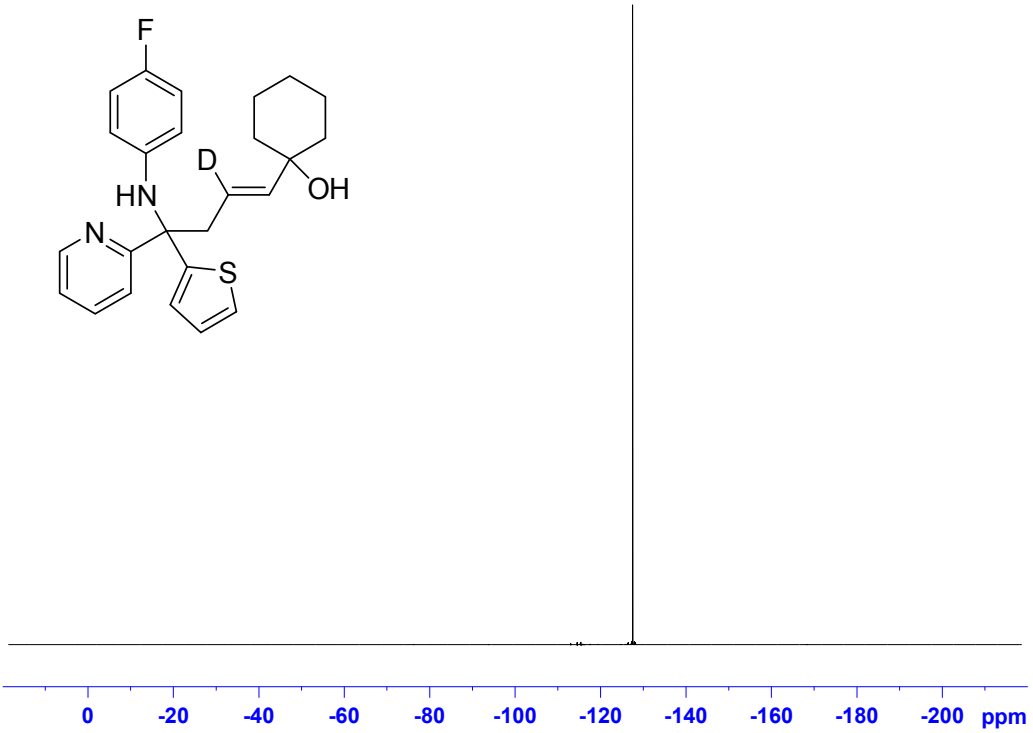
8a-d$_1$ (^{1}H NMR, $CDCl_3$, 600.13 MHz, 295 K)



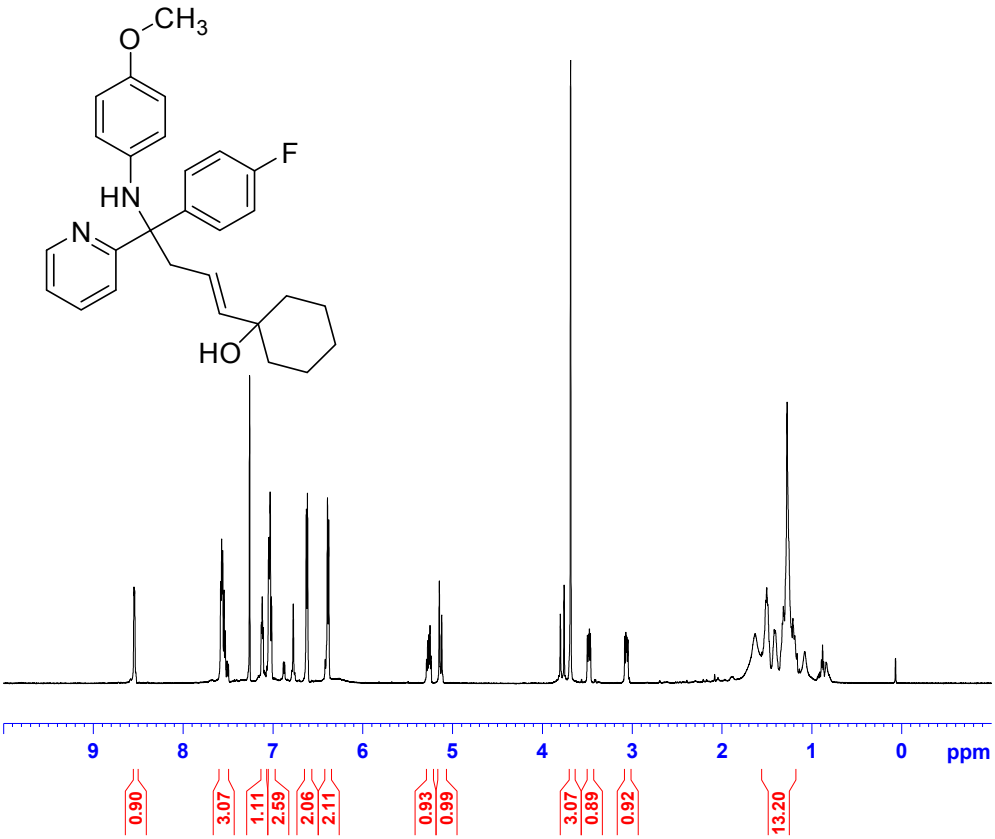
8a-d$_1$ (^{13}C{^{1}H} NMR, $CDCl_3$, 150.90 MHz, 295 K)



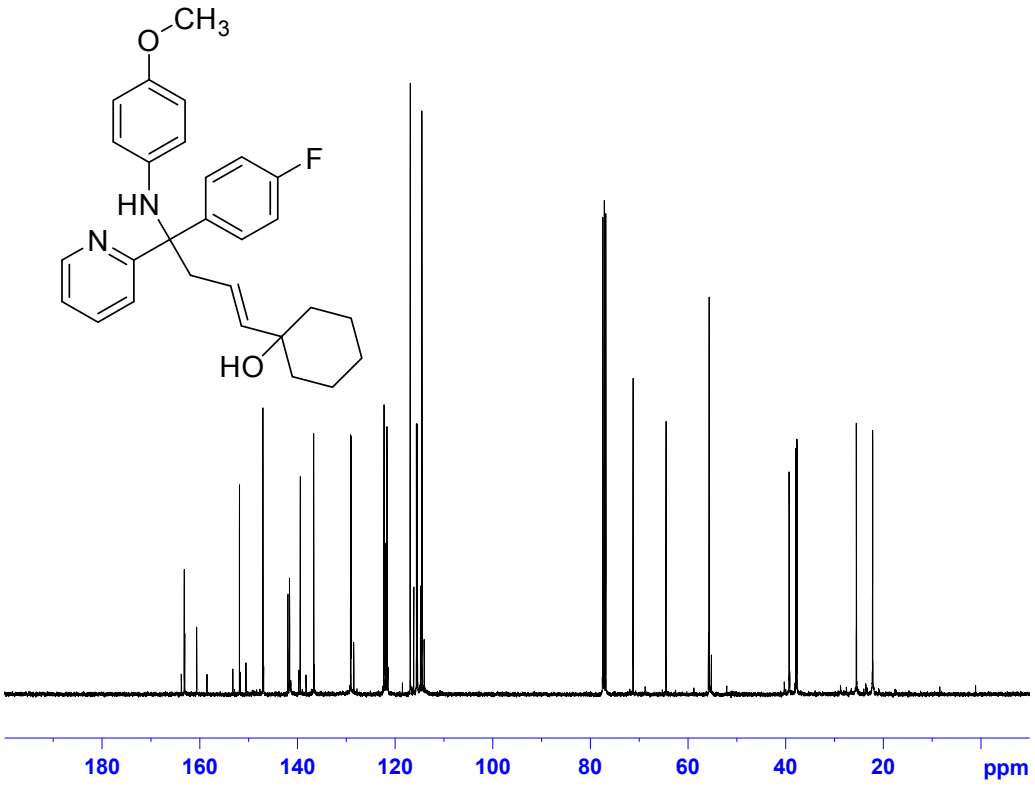
8a-d$_1$ (^{19}F{^{1}H} NMR, $CDCl_3$, 376.27 MHz, 297 K)



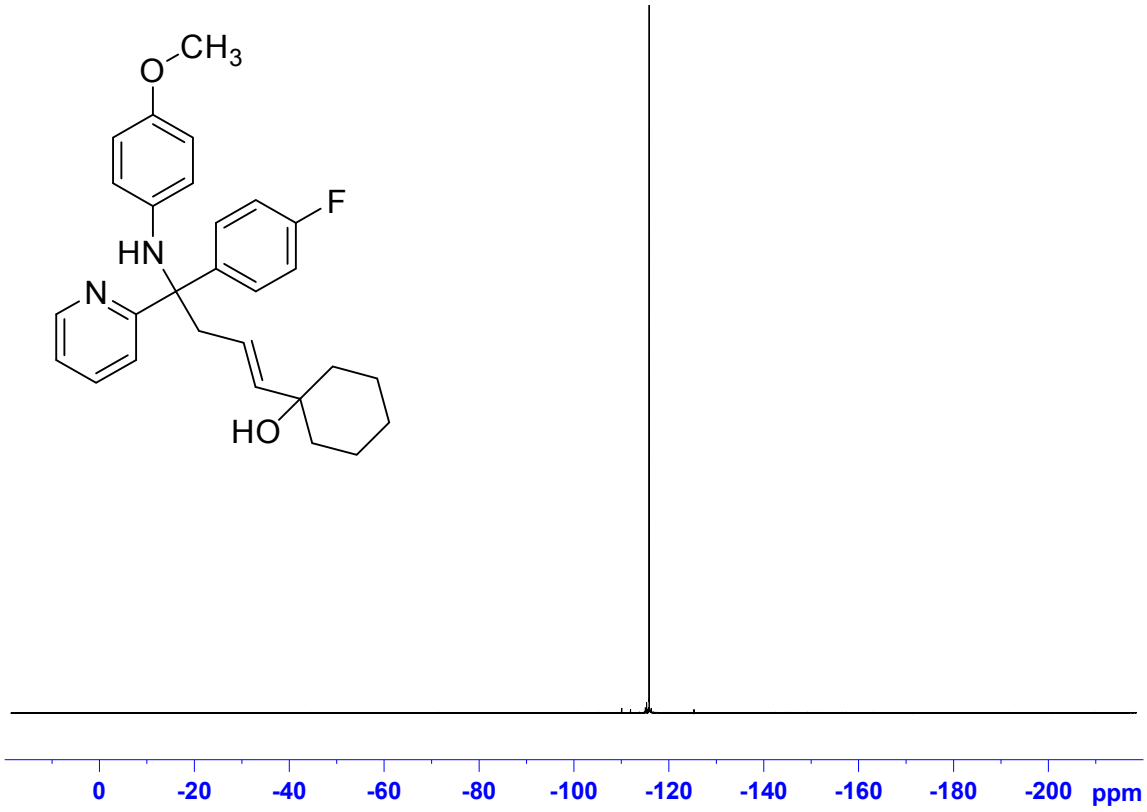
8b (^{1}H NMR, $CDCl_3$, 399.89 MHz, 297 K)



8b ($^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100.55 MHz, 298 K)



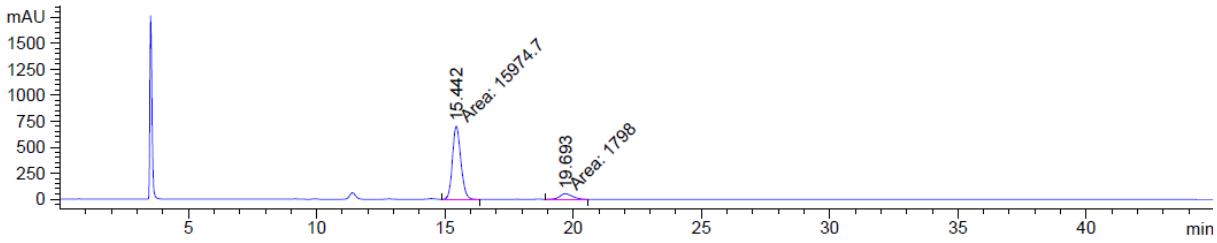
8b ($^{19}F\{^{1}H\}$ NMR, $CDCl_3$, 376.27 MHz, 297 K)



15. HPLC data

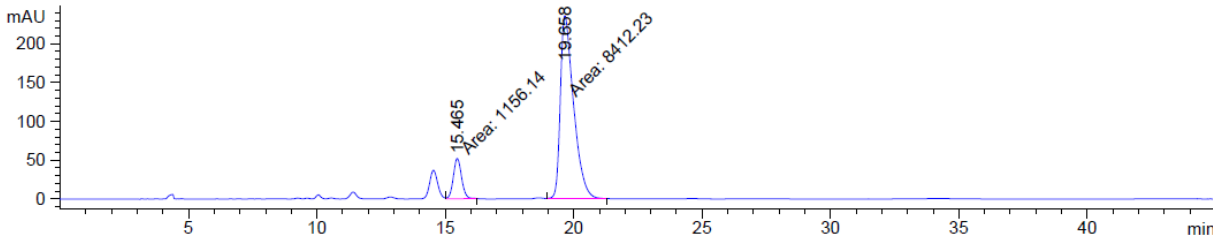
7b: HPLC: Column: AD-H, *n*-hexane:*iso*-propanol = 98:2, λ = 254 nm, flow rate 1 mL/min, 20 °C, $t_{(1)}$= 15.4 min, $t_{(2)}$= 19.7 min. (*S*)-1-Phenyl-2-propen-1-ol yields the product $t_{(1)}$ as major species.

7b from (*S*)-1-phenyl-2-propen-1-ol:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.442	MM	0.3782	1.59747e4	703.96783	89.8833
2	19.693	MM	0.5624	1798.00000	53.28172	10.1167
Totals :				1.77727e4	757.24955	

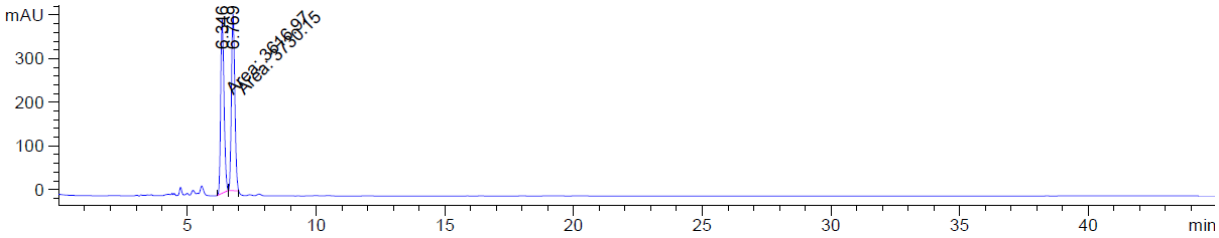
7b from (*R*)-1-phenyl-2-propen-1-ol:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.465	MM	0.3715	1156.13647	51.86187	12.0829
2	19.658	MM	0.5952	8412.22656	235.54973	87.9171
Totals :				9568.36304	287.41159	

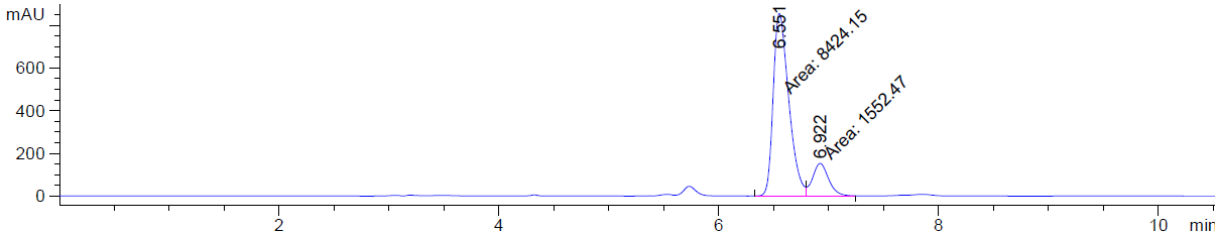
7c: HPLC: Column: AD-H, *n*-hexane:*iso*-propanol = 98:2, λ = 254 nm, flow rate 1 mL/min, 20 °C, $t_{(1)}$= 6.3 min, $t_{(2)}$= 6.8 min. (*S*)-1-Octen-3-ol yields the product $t_{(1)}$ as major species.

7c from racemic 1-octen-3-ol



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.346	MM	0.1507	3616.96997	400.00870	49.2298
2	6.769	MM	0.1536	3730.14697	404.71957	50.7702
Totals :				7347.11694	804.72827	

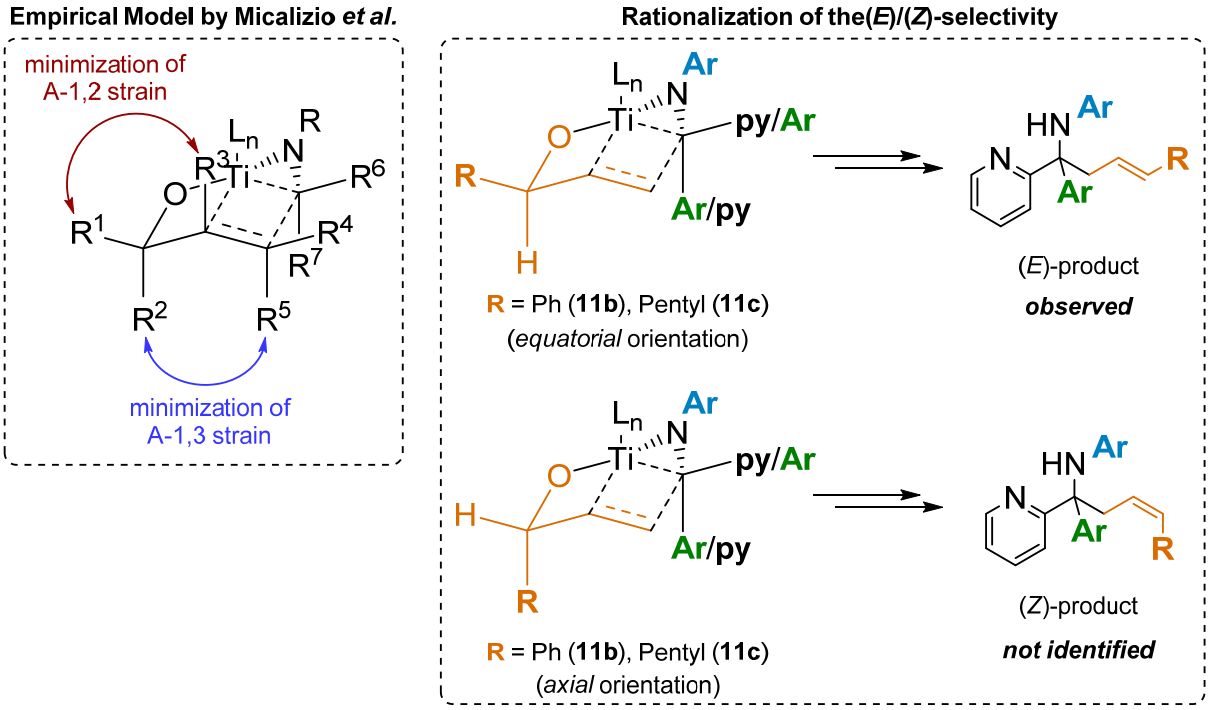
7c from (*S*)-1-octen-3-ol



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.551	MM	0.1639	8424.14648	856.37952	84.4389
2	6.922	MM	0.1685	1552.47021	153.58948	15.5611
Totals :				9976.61670	1009.96899	

16. Empirical model

Micalizio *et al.* proposed an empirical model for the prediction of (*E*)- and (*Z*)-selectivity in titanium-mediated coupling reactions.[24] The selectivity is governed by A-1,2 and A-1,3 strain interactions. However, since only monosubstituted allylic alkoxides were used in this study, only the axial and equatorial orientation of the alkoxide R-group was considered. Based on the model depicted below, and the isolation and characterization of the (*E*)-products **7b** and **7c** an equatorial orientation of the phenyl or pentyl group in the transition state seems likely.



A further discussion of the reaction mechanism, e.g. the mechanism for the partial chirality transfer in the reactions leading to **7b** and **7c** is not feasible at this point.

17. References

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